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1,5-Benzoxathiepin Derivatives. II.[1] Synthesis and Serotonin S_2-Receptor-Blocking Activity of Aminoalkyl-Substituted 3,4-Dihydro-2*H*-1,5-benzoxathiepin-3-ols and Related Compounds

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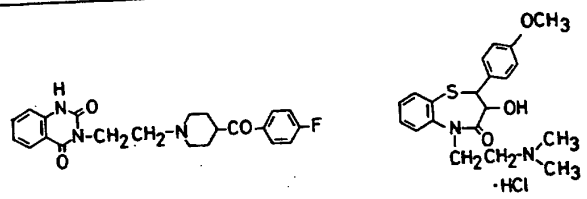
Novel 1,5-benzoxathiepin derivatives, 3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols with an aminoalkyl group at the 2-, 3- or 4-position, were synthesized and evaluated for serotonin S_2-receptor-blocking activity and adrenergic α_1-receptor-blocking activity. Methyl 4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates showed significant S_2-receptor-blocking activities. Structure–activity relationships (including the results of a conformational study and skeletal modifications) were examined. In the series of 1,5-benzoxathiepin, 1-benzoxepin and 1-benzothiepin derivatives, methyl *cis*-3-hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate hydrochloride (CV-5197) showed the most potent and the most selective S_2-receptor-blocking activity in the binding profile, and was chosen as a candidate for further pharmacological evaluation.

Keywords——seven-membered heterocycle; 1,5-benzoxathiepin derivative; aminoalkyl-substituted 3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol; serotonin S_2-receptor antagonist; structure–activity relationship; 1,5-benzoxathiepin derivative conformation; CV-5197

Serotonin (5-hydroxytryptamine, 5-HT) is known to act as a chemical mediator in a wide variety of physiological actions. Peroutka and Snyder demonstrated the existence of distinct populations of serotonin receptors, S_1 or 5-HT_1 and S_2 or 5-HT_2 receptors, based on the binding characteristics of radio-labeled serotonin and spiperone in rat brain homogenate, respectively.[2] Peripheral vascular serotonergic receptors have the pharmacological characteristics of receptors such as S_2-receptors in the central nervous systems.[3] Ketanserin, which is a potent and selective S_2-receptor antagonist, is a member of a new class of drugs possessing effective antihypertensive activity.[4] However, recent studies suggest that the antihypertensive effect of ketanserin in animal models is more related to its postsynaptic adrenergic α_1-receptor-blocking activity than to its antagonism of vascular S_2-receptors, and the apparent role of serotonin in hypertension is still uncertain.[5] Nevertheless, platelet aggregation due to serotonin is mediated through S_2-receptors.[6] Furthermore, serotonin has an amplifying effect on vascular and platelet actions, which is also mediated through S_2-receptors.[4,6,7] Thus, the selective antagonism of S_2-receptors might be important in preventing peripheral circulatory disorders in which vasoconstriction and platelet aggregation are suggested to be involved. In a study of the structure–activity relationships of S_2-receptor antagonists, no distinct structural relationships among serotonin and antagonists were found except for the essential amino function in the molecules.[8] Diltiazem, classified as a Ca antagonist having a structure with the seven-membered 1,5-benzothiazepine skeleton, caused reduction of the serotonin-induced contraction in isolated rabbit basilar artery, whereas such a reduction was diminished in the aorta.[9]



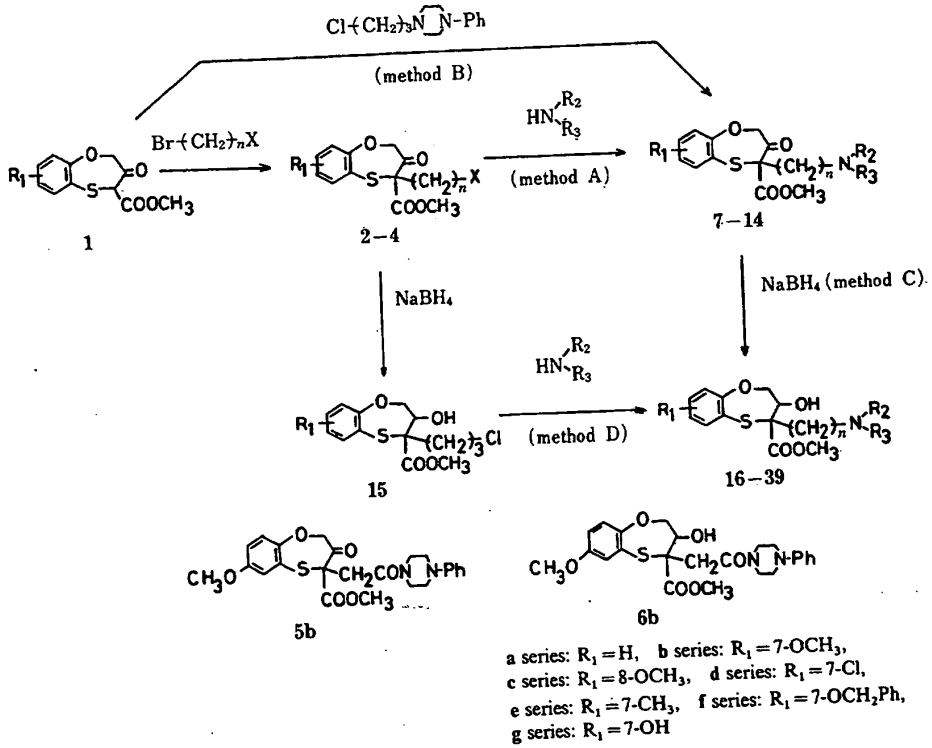
ketanserin diltiazem

Chart 1

With the aim of finding a novel S_2-receptor blocker, we synthesized 1,5-benzoxathiepin derivatives having structures analogous to 1,5-benzothiazepines and found that the 3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols with an aminoalkyl group at the 4-position showed significant S_2-receptor-blocking activities. In this paper, we report the syntheses of the 1,5-benzoxathiepins with an aminoalkyl group at the 2-, 3-, or 4-position and related compounds, and the structure–activity relationships of S_2-receptor-blocking activity.

Synthesis of Aminoalkyl-Substituted 1,5-Benzoxathiepin Derivatives and Related Compounds

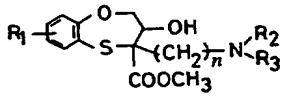
In the previous paper, we reported a novel synthetic route to the 1,5-benzoxathiepin skeleton and some modifications at its 2-, 3-, and 4-positions.[1] We first examined the introduction of an aminoalkyl group into the 4-position of methyl 3-oxo-3,4-dihydro-2*H*-1,5-



a series: R_1=H, b series: R_1=7-OCH_3, c series: R_1=8-OCH_3, d series: R_1=7-Cl, e series: R_1=7-CH_3, f series: R_1=7-OCH_2Ph, g series: R_1=7-OH

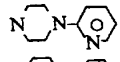
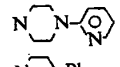
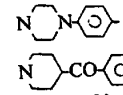
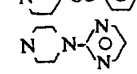
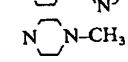
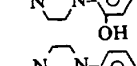
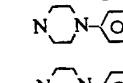
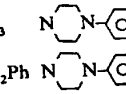
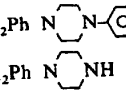
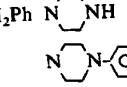
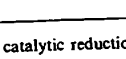
Chart 2

TABLE 1. Physicochemical Properties of Methyl 4-Aminoalkyl-Substituted 3-Hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (16—39)



Compd. No.	R_1	$N<^{R_2}_{R_3}$	n	Method[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
cis-**16b**	7-OCH_3	N-Ph	2	F	42	213—216	$C_{24}H_{30}N_2O_5S\cdot 2HCl$	54.24 (54.14)	6.07 6.08	5.27 5.29)
cis-**17a**	H	N-Ph	3	C	52	196—198	$C_{24}H_{30}N_2O_4S\cdot 2HCl$	55.92 (55.73)	6.26 6.15	5.45 5.51)
trans-**17a**	H	N-Ph	3	C	38	165—170	$C_{24}H_{30}N_2O_4S\cdot 2HCl\cdot 1/4\,H_2O$	55.43 (55.47)	6.30 6.19	5.39 5.40)
cis-**17b**	7-OCH_3	N-Ph	3	C D	47 56	154—155	$C_{25}H_{32}N_2O_5S\cdot HCl\cdot 2H_2O$	55.09 (55.46)	6.84 6.77	5.14 5.09)
trans-**17b**	7-OCH_3	N-Ph	3	C	31	140—145	$C_{25}H_{32}N_2O_5S\cdot HCl\cdot H_2O$	56.97 (56.67)	6.69 6.70	5.31 5.35)
cis-**17c**	8-OCH_3	N-Ph	3	C	46	195—198	$C_{25}H_{32}N_2O_5S\cdot HCl\cdot 1/4\,H_2O$	58.47 (58.43)	6.57 6.44	5.46 5.62)
trans-**17c**	8-OCH_3	N-Ph	3	C	30	170—175	$C_{25}H_{32}N_2O_5S\cdot 2HCl\cdot 1/2\,H_2O$	54.12 (54.08)	6.36 6.02	5.05 5.03)
cis-**17d**	7-Cl	N-Ph	3	C	42	205—207	$C_{24}H_{29}ClN_2O_4S\cdot 2HCl\cdot 1/2\,H_2O$	51.57 (51.77)	5.77 5.79	5.01 4.97)
trans-**17d**	7-Cl	N-Ph	3	C	38	150—160	$C_{24}H_{29}ClN_2O_4S\cdot 2HCl$	52.42 (52.24)	5.68 5.76	5.09 4.97)
cis-**17e**	7-CH_3	N-Ph	3	C	48	170—175	$C_{25}H_{32}N_2O_4S\cdot 2HCl$	56.70 (56.73)	6.47 6.54	5.01 5.04)
trans-**17e**	7-CH_3	N-Ph	3	C	33	145—155	$C_{25}H_{32}N_2O_4S\cdot 2HCl\cdot 1/4\,H_2O$	56.23 (56.39)	6.51 6.53	5.25 5.24)
cis-**17f**	7-OCH_2Ph	N-Ph	3	D	61	198—201	$C_{31}H_{38}N_2O_5S\cdot HCl$	63.62 (63.32)	6.37 6.41	4.79 4.52)
cis-**17g**	7-OH	N-Ph	3	E	64	207—209	$C_{24}H_{30}N_2O_5S$	62.86 (62.61)	6.59 6.50	6.11 5.88)
cis-**18b**	7-OCH_3	N-Ph	4	C	75	168—171	$C_{26}H_{34}N_2O_5S\cdot 2HCl$	55.81 (55.92)	6.49 6.54	5.01 5.04)
trans-**18b**	7-OCH_3	N-Ph	4	C	11	128—130	$C_{26}H_{34}N_2O_5S$	64.17 (64.32)	7.04 6.95	5.76 5.62)
cis-**19b**	7-OCH_3	N-Ph	5	C	22	125—128	$C_{27}H_{36}N_2O_5S\cdot HCl\cdot 1^1/_2\,H_2O$	57.48 (57.20)	7.14 6.98	4.97 4.94)
cis-**20b**	7-OCH_3	N-(2-Cl-Ph)	3	C	55	145—150	$C_{25}H_{31}ClN_2O_5S\cdot 2HCl\cdot 1/2\,H_2O$	50.98 (50.67)	5.82 6.12	4.76 4.61)
trans-**20b**	7-OCH_3	N-(2-Cl-Ph)	3	C	33	111—113	$C_{25}H_{31}ClN_2O_5S\cdot$	59.22 (59.28)	6.16 6.27	5.52 5.34)
cis-**21b**	7-OCH_3	N-(2-OCH$_3$-Ph)	3	C	50	140—145	$C_{26}H_{34}N_2O_6S\cdot HCl\cdot 2H_2O$	54.30 (54.57)	6.83 6.64	4.87 4.70)
trans-**21b**	7-OCH_3	N-(2-OCH$_3$-Ph)	3	C	20	170—175	$C_{26}H_{34}N_2O_6S\cdot 2HCl\cdot H_2O$	52.61 (52.99)	6.45 6.24	4.72 4.72)
cis-**22b**	7-OCH_3	N-(2,4-(OCH$_3$)$_2$-Ph)	3	C	55	185—193	$C_{26}H_{34}N_2O_6S\cdot 2HCl$	54.26 (54.56)	6.30 6.29	4.87 5.07)
trans-**22b**	7-OCH_3	N-(2,4-(OCH$_3$)$_2$-Ph)	3	C	22	178—182	$C_{26}H_{34}N_2O_6S\cdot 2HCl$	54.26 (54.05)	6.31 6.36	4.88 4.66)
cis-**23b**	7-CH_3	N-CHPh$_2$	3	C	65	133—135	$C_{32}H_{38}N_2O_5S$	68.30 (68.48)	6.81 6.73	4.98 4.97)

TABLE I. (continued)

Compd. No.	R_1	$N<^{R_2}_{R_3}$	n	Method[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
trans-**23b**	7-OCH_3		3	C	33	173—176	$C_{32}H_{38}N_2O_5S$	68.30 (68.34)	6.81 6.81	4.98 4.82)
cis-**24b**	7-OCH_3		3	C	63	173—176	$C_{24}H_{31}N_3O_5S \cdot 2HCl \cdot 1/2H_2O$	51.89 (51.96)	6.17 6.40	7.56 7.32)
trans-**24b**	7-OCH_3		3	C	25	222—225	$C_{24}H_{31}N_3O_5S \cdot 2HCl$	52.74 (52.31)	6.09 6.02	7.69 7.65)
cis-**25b**	7-OCH_3		3	D	51	135—140	$C_{26}H_{33}NO_5S \cdot HCl \cdot 1/2H_2O$	60.39 (60.48)	6.82 6.84	2.71 2.70)
cis-**26b**	7-OCH_3		3	D	36	140—150	$C_{25}H_{31}FN_2O_5S \cdot 2HCl \cdot 1/2H_2O$	52.44 (52.71)	5.90 5.82	4.89 4.79)
cis-**27b**	7-OCH_3		3	D	43	150—153	$C_{27}H_{32}FNO_6S \cdot HCl \cdot H_2O$	56.68 (56.71)	6.17 6.08	2.45 2.46)
cis-**28b**	7-OCH_3		3	D	24	210—213	$C_{23}H_{30}N_4O_5S \cdot 2HCl \cdot H_2O$	48.85 (48.94)	6.06 5.84	9.91 9.99)
cis-**29b**	7-OCH_3		3	D	35	142—145	$C_{20}H_{30}N_2O_5S \cdot 1/2H_2O$	57.29 (57.45)	7.45 7.40	6.68 6.71)
cis-**30b**	7-OCH_3		3	D	47	205—210	$C_{19}H_{29}NO_6S \cdot HCl$	52.59 (52.57)	6.50 6.72	3.23 3.19)
cis-**31b**	7-OCH_3		3	D	34	185—188	$C_{19}H_{29}NO_5S \cdot HCl$	54.34 (54.07)	7.20 7.23	3.34 3.34)
cis-**32b**	7-OCH_3		3	D	41	—[b]	$C_{26}H_{35}NO_7S \cdot HCl \cdot 1/2H_2O$	56.67 (56.68)	6.77 6.97	2.54 2.51)
cis-**33b**	7-OCH_3		3	D	50	175—190	$C_{25}H_{32}N_2O_6S \cdot 2HCl \cdot 1/2H_2O$	52.63 (52.91)	6.18 5.94	4.91 4.95)
cis-**34b**	7-OCH_3		3	D	65	175—180	$C_{25}H_{32}N_2O_6S \cdot 2HCl \cdot H_2O$	51.81 (52.00)	6.26 6.02	4.83 4.72)
cis-**35b**	7-OCH_3		3	D	50	240—245	$C_{25}H_{32}N_2O_6S \cdot 2HCl$	53.43 (53.20)	6.10 5.97	4.99 5.21)
cis-**36f**	7-OCH_2Ph		3	D	57	247—251	$C_{31}H_{36}N_2O_6S \cdot HCl$	61.93 (61.91)	6.20 6.01	4.66 4.65)
cis-**37f**	7-OCH_2Ph		3	F	64	193—200	$C_{25}H_{32}N_2O_5S \cdot 2HCl \cdot 1/2H_2O$	54.15 (54.10)	6.36 6.30	5.05 5.11)
cis-**38g**	7-OH		3	E	72	226—229	$C_{24}H_{30}N_2O_6S$	60.74 (60.47)	6.37 6.39	5.90 5.71)
cis-**39g**	7-OH		3	E	90	233—240	$C_{18}H_{26}N_2O_5S \cdot 2HCl$	47.47 (47.19)	6.20 6.36	6.15 5.86)

a) Method E, catalytic reduction of the corresponding *O*-benzyl ether. Method F, see experimental section. *b*) Amorphous powder.

benzoxathiepin-4-carboxylates (**1a**—**f**) by alkylation of the reactive methine carbon (Chart 2). The ketoesters (**1a**—**f**) were alkylated with ω-halogenoalkyl bromides having a side chain of various lengths ($n=3$—5) in refluxing acetonitrile by using potassium carbonate and a catalytic amount of potassium iodide to yield a mixture of the desired *C*-alkylated compounds (30—40%) and *O*-alkylated enole ethers (10—20%) as a by-product. Chromatographic separation of the reaction mixture gave methyl 4-(ω-halogenoalkyl)-3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**2**—**4**). The 4-[2-oxo-2-(4-phenyl-1-piperazinyl)ethyl] derivative (**5b**) was prepared by alkylation of **1b** with 1-chloroacetyl-4-phenylpiperazine in 69% yield. Conversion of the halogeno moiety of **2**—**4** into the amino group by sub-

stitution with some amines was carried out by heating in *N*,*N*-dimethylformamide (DMF) at 70 °C in the presence of potassium carbonate and potassium iodide to give methyl 4-aminoalkyl-substituted 3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**7**—**14**) in fairly good yields (58—76%) (method A). Direct introduction of an *N*-phenylpiperazinylpropyl moiety into the 4-position of **1** by alkylation using 4-phenyl-1-piperazinylpropyl chloride gave *N*-phenylpiperazinylpropyl derivatives (**7a**—**e**) in 18—31% yields (method B). Reduction of **7**—**14** with sodium borohydride ($NaBH_4$) in an ice-cooled solution of methanol and tetrahydrofuran (THF), and subsequent separation of the resulting stereoisomeric products by column chromatography on silica gel gave methyl *cis*- and *trans*-4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**17**—**24**) (method C) (Table I). The configurational nomenclature in this paper refers to the relative configuration between the 3-hydroxy group and the 2- or 4-substituent with higher priority. In each case, $NaBH_4$ reduction produced predominantly *cis*-alcohols over *trans*-isomers in the range of 1 : 1—2 : 1 ratios. Similar $NaBH_4$ reduction of **2b** and **2f** afforded *cis*-4-chloropropyl-3-ols (*cis*-**15b**, 63% and *cis*-**15f**, 50%) and *trans*-alcohols (*trans*-**15b**, 25% and *trans*-**15f**, 30%), respectively. Substitution of *cis*-**15b** and *cis*-**15f** with various kinds of amines gave *cis*-alcohols with a modified amino group (*cis*-**25**—*cis*-**36**) (method D). The *N*-phenylpiperazinylethyl derivative (*cis*-**16b**) was synthesized by $NaBH_4$ reduction of **5b**, followed by selective reduction of the amide moiety with sodium monoacetoxyborohydride[10] in boiling THF. 7-Hydroxy derivatives (*cis*-**17g**, *cis*-**36g**, and *cis*-**39g**) were obtained by catalytic reduction of the corresponding 7-benzyloxy derivatives (*cis*-**17f**, *cis*-**36f**, and *cis*-**37f**) using palladium black as a catalyst in ethanol containing hydrochloric acid (method E). The stereochemistries of the compounds bearing substituents at the 3- and 4-positions were determined on the basis of various data including X-ray crystallographic analysis, proton nuclear magnetic resonance (^{1}H-NMR) spectral data and *Rf* values of each stereoisomer. The physicochemical properties of methyl *cis*- and *trans*-4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**16**—**39**) thus obtained are summarized in Table I.

The *N*-phenylpiperazinylpropyl group was introduced into the 2-position by converting the ester group of methyl 3-(3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-2-yl)propionates (**40b** and **40c**)[11] in three steps (Chart 3). Reduction of **40b** with $NaBH_4$ and subsequent chromatographic separation gave *cis*-**41b** (47%) and *trans*-**41b** (36%). On the other hand, similar reduction of **40c** gave *cis*-**41c** (86%) and a minor product (7%) which could not be

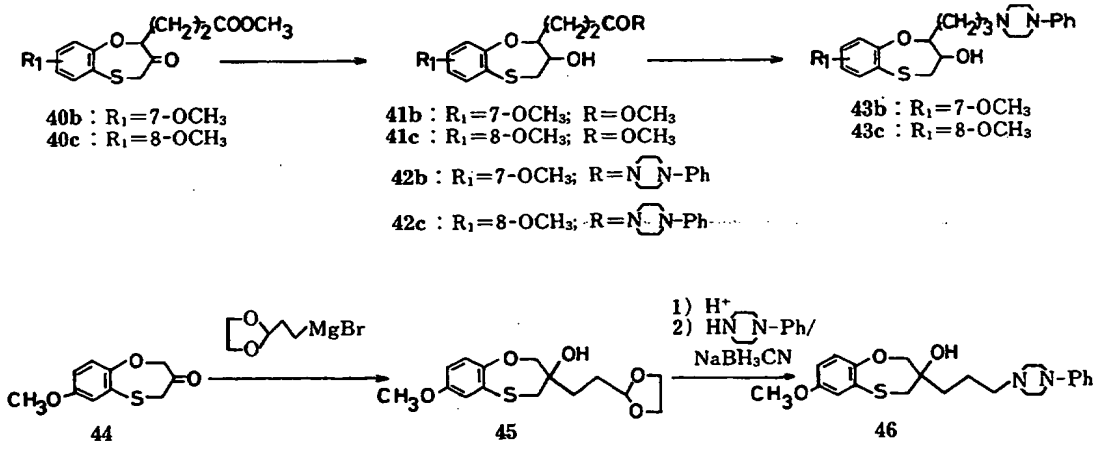


Chart 3

identified as *trans*-**41c**. Heating a mixture of the ester (*cis*-**41b**) and *N*-phenylpiperazine at 90 °C for 5 h afforded the amide (*cis*-**42b**), which was reduced with lithium aluminum hydride ($LiAlH_4$) in THF to yield *cis*-7-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-**43b**). Similarly, *trans*-**43b** and *cis*-**43c** were prepared *via* the amides (*trans*-**42b** and *cis*-**42c**).

Grignard reaction of 7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (**44**)[11] with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide[11] in THF gave 3-(1,3-dioxolan-2-yl)ethyl-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**45**) in 82% yield. Next, deprotection of the acetal group to aldehyde by treatment with dilute hydrochloric acid and subsequent reductive amination with *N*-phenylpiperazine using sodium cyanoborohydride afforded 7-methoxy-3-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**46**) in 57% yield (Chart 3).

The compound (**50b**) lacking the 4-methoxycarbonyl group in *cis*-**17b**, which showed the most potent antagonistic activity against S_2-receptors, was prepared in several steps from **2b** as illustrated in Chart 4. Heating **2b** in DMF at 100 °C for 6 h in the presence of aqueous lithium chloride afforded 4-(3-chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (**47b**) in 48% yield. Either $NaBH_4$ reduction of **47b** and subsequent replacement of the chloro group by *N*-phenylpiperazine or initial amination of **47b** and subsequent $NaBH_4$ reduction gave the same single product, the structure of which was confirmed as the *cis*-isomer (*cis*-**50b**) by X-ray crystallographic analysis. In order to prepare the *trans*-isomer, we examined another synthetic route and found that decarboxylation of *cis*-4-(3-chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylic acid (*cis*-**51b**) obtained by alkaline hydrolysis of *cis*-**15b** with heating at 180 °C for 30 min gave *trans*-**48b** with stereochemical retention of the 3-hydroxy and 4-(3-chloropropyl) groups in 16% yield. Subsequent substitution reaction of *trans*-**48b** with *N*-phenylpiperazine gave *trans*-**50b**.

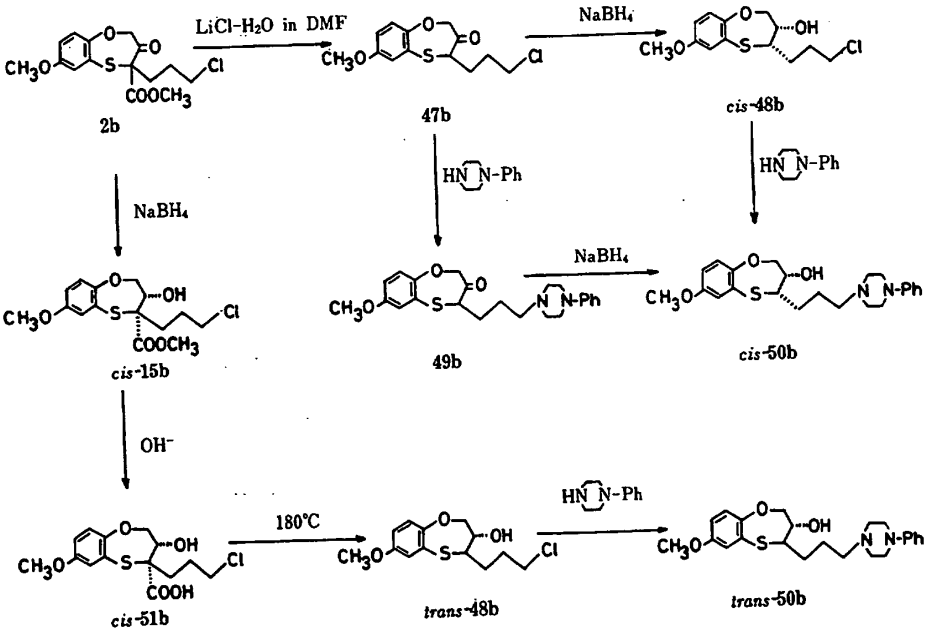


Chart 4

Removal of the 3-hydroxy group from *cis*-**17b** was unsuccessful. Tosylation of *cis*-**17b** with tosyl chloride in pyridine and subsequent catalytic reduction of the crude product using 10% palladium charcoal in ethyl acetate yielded two isomeric products (**52** and **53**) which were also obtained by reduction of *cis*-**15b** with red phosphorus and hydriodic acid in aqueous acetic acid, followed by treatment with *N*-phenylpiperazine. The infrared (IR) spectra of **52** and **53** showed similar absorptions to each other. The 400 MHz NMR spectrum of **52** exhibited two double doublets at δ 4.115 (J=12.0, 5.4 Hz) and 4.263 (J=12.0, 2.1 Hz) due to methylenic protons adjacent to the oxygen atom and a sextet (ddd) at δ 3.612 (J=2.1, 5.4, 9.5 Hz) assignable to the methine proton attached to the carbon bearing the sulfur atom. On irradiation at δ 3.612, the two double doublets were transformed into two doublets with geminal coupling (J=12.0 Hz). The ^{1}H-NMR spectrum of **53** showed similar signals with ABX coupling at δ 4.184 (1H, dd, J=12.2, 2.0 Hz), 4.439 (1H, dd, J=12.2, 4.2 Hz), and 3.599 (1H, ddd, J=2.1, 4.2, 9.8 Hz). These results indicate the presence of the $OCH_2\underset{|}{C}HS$ group and the absence of the OCH_2CH_2 group as partial structures of **52** and **53**. Thus, the structures of **52** and **53** were assigned as isomeric methyl 5-(4-phenyl-1-piperazinyl)-2-(6-methoxy-1,4-benzoxathian-3-yl)pentanoates, which might be produced by rearrangement involving the episulfonium ion intermediates[12] generated by elimination of the hydroxy group at the 3-position. Compound **58**, which lacks the 3-hydroxy group in addition to the 4-ester of *cis*-**17b**, was synthesized as illustrated in Chart 5. Grignard reaction of 3-chloropropanal with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide in THF gave 1-chloro-5-(1,3-dioxolan-2-yl)pentan-3-ol (**54**) in 73% yield. Then **54** was converted into 5-(1,3-dioxolan-2-yl)-3-mesyloxypentyl benzoate (**55**) by the reaction of **54** with sodium benzoate in DMF, followed by mesylation.

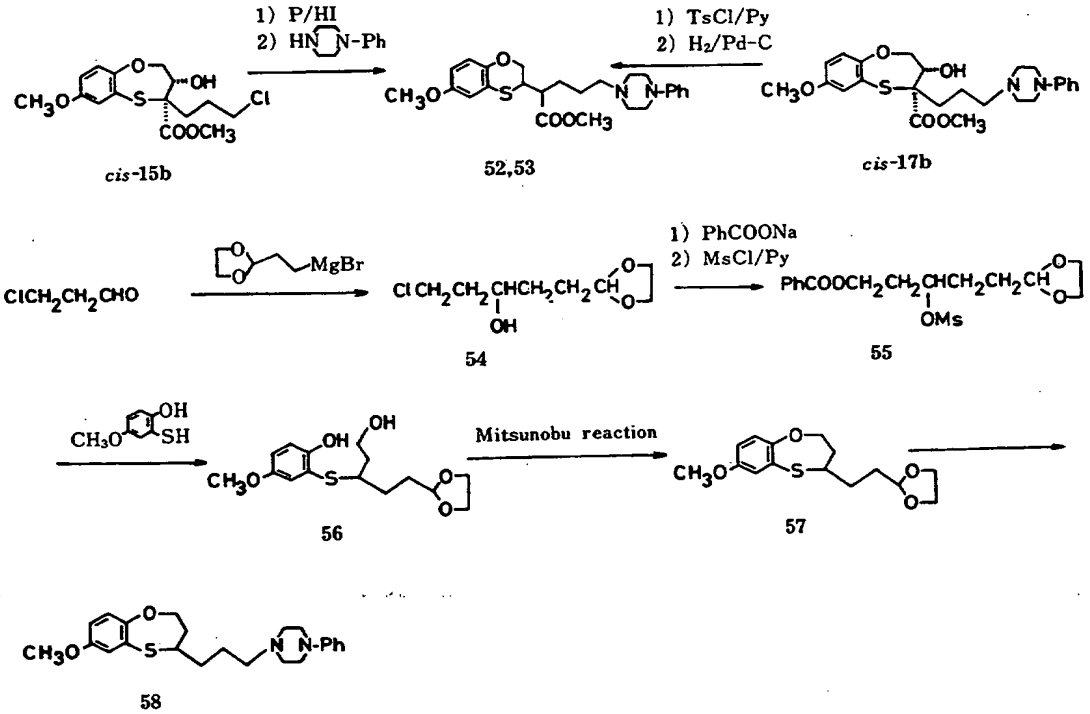
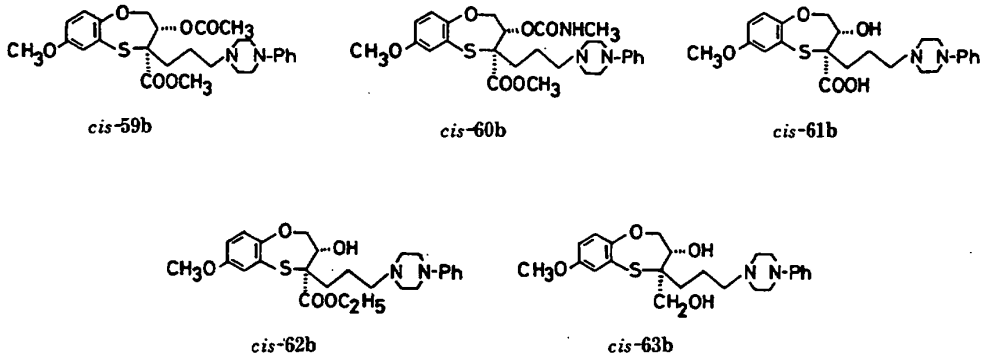


Chart 5

Treatment of **55** with 4-methoxy-2-mercaptophenol and subsequent alkaline hydrolysis gave the precursor (**56**) in 43% yield from **55**. Ring closure of **56** was conducted by means of the Mitsunobu reaction[13] using triphenylphosphine and ethyl azodiformate in toluene to afford 7-methoxy-4-[2-(1,3-dioxolan-2-yl)ethyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin (**57**, 71%), which was converted into the desired 7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin (**58**, 51%) by reductive amination after deprotection of the acetal group of **57**.

Modifications of the 3-hydroxy and the 4-ester groups of *cis*-**17b** were done by *O*-acetylation, *O*-carbamoylation using methyl isocyanate, alkaline hydrolysis, esterification of the resulting 4-carboxylic acid with diethyl sulfate, and lithium aluminum hydride reduction, to give the *O*-acetate (*cis*-**59b**), the 3-*N*-methylcarbamoyloxy derivative (*cis*-**60b**), 4-carboxylic acid (*cis*-**61b**), the 4-ethyl ester (*cis*-**62b**) and the 4-methanol (*cis*-**63b**), respectively (Chart 6).

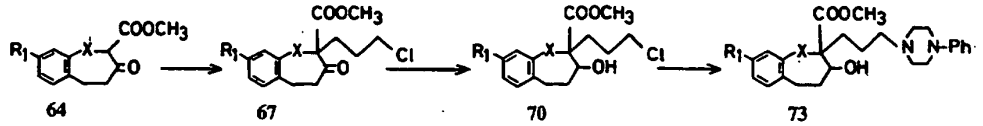


cis-**59b** *cis*-**60b** *cis*-**61b**

cis-**62b** *cis*-**63b**

Chart 6

We also tried to prepare the 1-benzoxepin and 1-benzothiepin analogs of *cis*-**17b** in order to clarify the pharmacological significance of the hetero atoms in the 1,5-benzoxathiepin ring (Chart 7). Methyl 8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (**64**) was obtained by Dieckmann reaction of methyl 3-(4-methoxy-2-methoxycarbonylmethyloxy)phenylpropionate according to the method described by Huckle *et al.*[14] Methyl 3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylates (**65** and **66**) were prepared by similar Dieckmann reaction according to the procedure of Huckle *et al.*[14] *via* the Newman's reaction[15] of methyl 2-hydroxyphenylpropionates. The syntheses of *N*-phenylpiperazinylpropyl-substituted 1-benzoxepin and 1-benzothiepin derivatives (**73**, **74**, and **75**) from the ketoesters (**64**, **65**, and **66**) were done by methods similar to those described for 1,5-benzoxathiepin derivatives, involving alkylation with 3-bromo-1-chloropropane, subsequent $NaBH_4$ reduction and finally substitution with *N*-phenylpiperazine (Chart 7) (Table II).

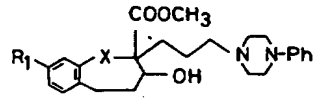


64 **67** **70** **73**
65 **68** **71** **74**
66 **69** **72** **75**

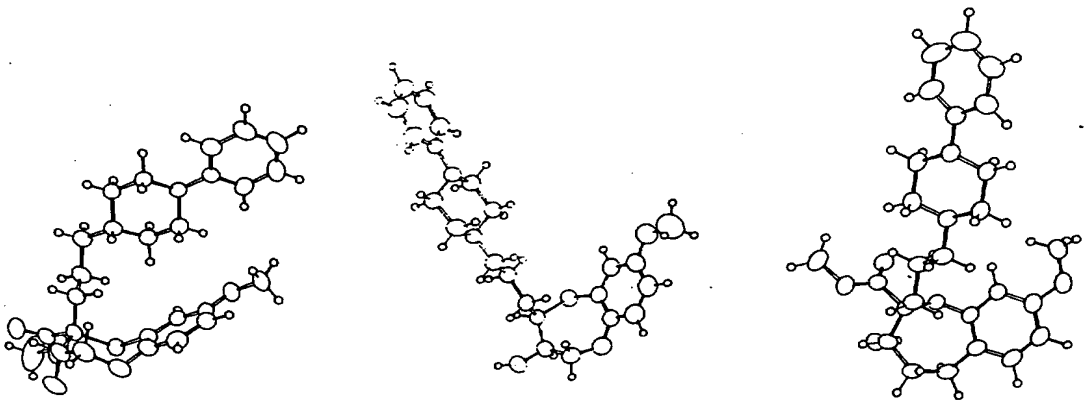
64, 67, 70, 73: $R_1 = OCH_3$; X=O
65, 68, 71, 74: $R_1 = H$; X=S
66, 69, 72, 75: $R_1 = OCH_3$; X=S

Chart 7

TABLE II. Physicochemical Properties of *N*-Phenylpiperazinylpropyl-Substituted 1-Benzoxepin and 1-Benzothiepin Derivatives (73—75)



Compd. No.	R_1	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
cis-**73**	OCH_3	O	47	126—128	$C_{26}H_{34}N_2O_5$	68.70 (68.42	7.54 7.62	6.16 6.02)
trans-**73**	OCH_3	O	72	140—155	$C_{26}H_{34}N_2O_5 \cdot 2HCl$	59.20 (59.12	6.88 6.96	5.31 5.23)
cis-**74**	H	S	60	152—154	$C_{25}H_{32}N_2O_3S$	68.15 (68.40	7.32 7.34	6.36 6.36)
cis-**75**	OCH_3	S	80	145—150	$C_{26}H_{34}N_2O_4S \cdot HCl \cdot 1/2H_2O$	60.51 (60.39	7.03 7.36	5.43 5.49)



cis-**17b**·HCl (CV-5197)[a] *cis*-**50b** *cis*-**73**

Fig. 1. X-Ray Structures of *cis*-**17b**·HCl, *cis*-**50b**, and *cis*-**73**
a) Shown without Cl^-.

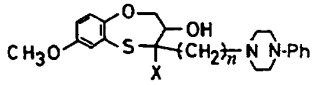
In the case of 1-benzothiepin derivatives, the hydride reduction of the 3-carbonyl moiety gave exclusively *cis*-alcohols (*cis*-**71** and *cis*-**72**) without detectable stereoisomers on thin-layer chromatography (TLC). The configurations of these compounds were determined by X-ray chrystallographic analysis of *cis*-**71** and comparison of the 400 MHz NMR spectral data of the products (**71** and **72**).

Configurations and Conformations of 1,5-Benzoxathiepin Derivatives and R lated Compounds

The conformations of seven-membered compounds have been investigated theoretically and experimentally from the viewpoint of interconversion and pseudorotation.[16,17]

We first determined the configurations of *cis*-**17b**, *cis*-**50b**, *cis*-**58b**, *cis*-**71**, and *cis*-**73** by X-ray crystallographic analysis and then examined the conformations in solution based on 400 MHz NMR spectra data. The X-ray results have shown that the chair form of the seven-membered ring is the common conformation for 1,5-benzoxathiepin (*cis*-**17b**, *cis*-**50b**, and *cis*-**58b**), 1-benzoxepin (*cis*-**73**), and 1-benzothiepin (*cis*-**71**) derivatives (Fig. 1). The most striking

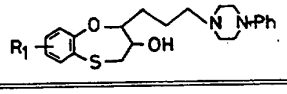
TABLE III. Selected 400 MHz NMR Spectral Data for 4-(4-Phenyl-1-piperazinyl)alkyl-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols



Compd. No.	X	*n*	Salt	NMR (DMSO-d_6)[a]					
				Chemical shift δ (ppm)			Coupling constant (Hz)		
				C_2-H_a	C_2-H_b	C_3-H	$J_{2a,3}$	$J_{2b,3}$	$J_{3,4}$
cis-**16b**	$COOCH_3$	2	2HCl	4.022	4.168	4.080	2.7	6.1	—
cis-**17b**	$COOCH_3$	3	HCl	3.873	4.155	3.999	0—1.0	4.6	—
cis-**17b**	$COOCH_3$	3	Free base	3.843	4.249	4.078	0—1.0	3.4	—
trans-**17b**	$COOCH_3$	3	HCl	3.794	4.107	4.383	8.4	3.8	—
cis-**18b**	$COOCH_3$	4	2HCl	3.920	4.151	4.017	2.3	5.6	—
trans-**18b**	$COOCH_3$	4	2HCl	3.783	4.063	4.314	7.8	3.7	—
cis-**19b**	$COOCH_3$	5	HCl	3.913	4.149	4.011	2.3	5.5	—
cis-**50b**	H	3	2HCl	3.776	4.017	4.152	8.5	3.8	3.8[b]
trans-**50b**	H	3	2HCl	3.855	4.329	3.785	4.9	2.8	7.7[c]

a) *cis*-**17b** (free base) was determined in $CDCl_3$ solution. *b*) δ 3.206 ppm (C_4-H). *c*) δ 3.031 ppm (C_4-H).

TABLE IV. Selected 400 MHz NMR Spectral Data for 2-[3-(4-Phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols

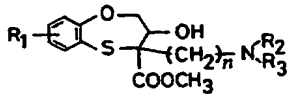


Compd. No.	R_1	NMR ($CDCl_3$)						
		Chemical shift δ (ppm)				Coupling constant (Hz)		
		C_2-H	C_3-H	C_4-H_a	C_4-H_b	$J_{2,3}$	$J_{3,4a}$	$J_{3,4b}$
cis-**43b**	7-OCH_3	3.609	3.975	2.953	3.039	0—1.0	2.1	5.4
trans-**43b**	7-OCH_3	3.96	3.96	2.735	3.534	—[a]	4.8	2.3
cis-**43c**	8-OCH_3	3.668	3.970	2.886	2.966	0—1.0	2.1	5.4

a) Not determined.

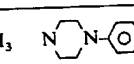
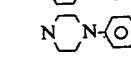
characteristic of *cis*-**17b** is the folded conformation of the whole molecule and the quasi-axial orientation of the sterically bulky *N*-phenylpiperazinylpropyl substituent. The 400 MHz NMR spectral data of the 4-[3-(4-phenyl-1-piperazinyl)propyl]-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin derivatives also support the occurrence of solution conformations that are similar to the solid state conformations, except in the case of *trans*-**50b** (Table III). The rather large coupling constant in *trans*-**17b** ($J_{2a,3}$ = 8.4 Hz) suggests the presence of a quasi-equatorial 3-hydroxy group in *trans*-**17b**, while the small values in *cis*-**17b** ($J_{2a,3}$ = 0—1.0 Hz and $J_{2b,3}$ = 4.6 Hz) indicate a major contribution of a conformation similar to the X-ray conformation in solution. The excellent agreement of the correlative *J* values of *cis*-**50b** and *trans*-**17b** indicates that these compounds possess similar conformations except for the structural difference of the absence or presence of the 4-ester moiety. However, the discrepancy between the *J* values in the NMR spectral data of *trans*-**50b** and *cis*-**17b** suggests that the major conformer of *trans*-**50b** differs from the X-ray conformer of *cis*-**17b**. The $J_{3,4}$

TABLE V. Biological Activities of Methyl 4-Aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates



Compd. No.	R_1	$N<^{R_2}_{R_3}$	n	Serotonin S_2-blocking activity[a]			Adrenaline α_1-blocking activity[b]	
				10^{-5}	10^{-6}	10^{-7} M	10^{-5}	10^{-6} M
cis-**16b**	7-OCH_3	N N–Ph	2	68			80	
cis-**17a**	H	N N–Ph	3	100	77	3	100	30
trans-**17a**	H	N N–Ph	3	100	18		100	75
cis-**17b**	7-OCH_3	N N–Ph	3		100	77	5	
trans-**17b**	7-OCH_3	N N–Ph	3	100	89	15	66	
cis-**17c**	8-OCH_3	N N–Ph	3	92	71	3	31	
trans-**17c**	8-OCH_3	N N–Ph	3	96	28		53	
cis-**17d**	7-Cl	N N–Ph	3	100	85	31	45	
trans-**17d**	7-Cl	N N–Ph	3	100	67	12	70	
cis-**17e**	7-CH_3	N N–Ph	3	100	77	40	35	
trans-**17e**	7-CH_3	N N–Ph	3	100	27	0	58	
cis-**17g**	7-OH	N N–Ph	3	79	16		0	
cis-**18b**	7-OCH_3	N N–Ph	4	66			95	
trans-**18b**	7-OCH_3	N N–Ph	4	66	35		90	
cis-**19b**	7-OCH_3	N N–Ph	5	56			90	
cis-**20b**	7-OCH_3	N N–(o-Cl)	3	94	35		47	
cis-**21b**	7-OCH_3	N N–(o-OCH_3)	3	88	12		100	28
cis-**24b**	7-OCH_3	N N–(o-N)	3	100	77	55	100	18
cis-**25b**	7-OCH_3	N N–Ph	3	100	88	25	40	
cis-**26b**	7-OCH_3	N N–(o-F)	3	100	99	12	30	
cis-**27b**	7-OCH_3	N CO–(o-F)	3	100	88	50	100	
cis-**28b**	7-OCH_3	N N–(o-N)	3	68			0	
cis-**32b**	7-OCH_3	$N(CH_3)$-$(CH_2)_2$-(o-OCH_3)	3	83	27		15	
cis-**33b**	7-OCH_3	N N–(o-OH)	3	100	12		55	
cis-**34b**	7-OCH_3	N N–(o-OH)	3	100	36	16	10	

TABLE V. (continued)

Compd. No.	R_1	$N<^{R_2}_{R_3}$	n	Serotonin S_2-blocking activity[a]			Adrenaline α_1-blocking activity[b]	
				10^{-5}	10^{-6}	10^{-7} M	10^{-5}	10^{-6} M
cis-**35b**	7-OCH_3		3	100	100	79	56	
cis-**38g**	7-OH		3	100	0		8	

a) % inhibition of 5-HT-induced contraction in pig coronary artery. *b*) % inhibition of norepinephrine-induced contraction in rabbit aorta.

TABLE VI. Biological Activities of 3-(4-Phenyl-1-piperazinyl)propyl-Substituted 3,4-Dihydro-2*H*-1,5-benzoxathiepin Derivatives and Related Analogs

Compd. No.	Serotonin S_2-blocking activity[a]			Adrenaline α_1-blocking activity[b]
	10^{-5}	10^{-6}	10^{-7} M	10^{-5} M
7b	100	80	2	63
cis-**43b**	56	13		50
trans-**43b**	42	0		77
cis-**43c**	100	63		53
46	25	0		99
cis-**50b**	99	35		50
trans-**50b**	72			55
58	58			60
cis-**59b**	100	92	19	40
cis-**60b**	100	47		72
cis-**62b**	100	83	19	0
cis-**63b**	90	17	0	50
cis-**73**	100			44
trans-**73**	100	24		62
cis-**74**	96	60		36
cis-**75**	100	69		31

a) % inhibition of 5-HT-induced contraction in pig coronary artery. *b*) % inhibition of norepinephrine-induced contraction in rabbit aorta.

value (7.7 Hz) of *trans*-**50b** suggests a substantial contribution of quasi-equatorial orientation of the *N*-phenylpiperazinylpropyl group at the 4-position. In the case of the derivatives with a side chain of various lengths (**16**, **18** and **19**), it was deduced that the main conformation of each stereoisomer was similar to that found for the corresponding isomer of **17b** on the basis of the NMR spectral data, supposing the half-chair conformation for the seven-membered ring. On the other hand, the equatorial orientation of the *N*-phenylpiperazinylpropyl moiety at the 2-position was estimated from the NMR spectral data of *cis*-**43b**, **c** and *trans*-**43b** (Table IV). X-ray crystallographic analyses and the NMR spectral data of 1-benzoxepin (**73**) and 1-benzothiepin (**74** and **75**) derivatives indicated that these compounds also had major conformers similar to those observed in **17b**. The main contribution of *trans*-1,2-diaxial orientation of the sterically bulky substituents for *cis*-**17b** in contrast with *trans*-**50b** is readily rationalizable in terms of the stabilizing effect associated with the favorable hydrogen bonding between the 3-hydroxy function and the 4-ester carbonyl in *cis*-**17b** compared with

trans-**50b**, lacking the ester group.

Biological Results and Discussion

The S_2-receptor-blocking activity and selectivity toward S_2-receptors over adrenergic α_1-receptors of the aminoalkyl-substituted 1,5-benzoxathiepin derivatives and related compounds synthesized in this paper were evaluated in terms of ability to antagonize serotonin-induced contraction in the isolated pig coronary artery and to block norepinephrine-induced contraction in the isolated rabbit aorta. The results of *in vitro* evaluation are shown in Tables V and VI.

Methyl 4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates showed significant S_2-receptor-blocking activities. The inhibitory potency for serotonin-induced contraction increased in the order of $3>2$, $4>5$ of side chain length (n). The substituents on the benzene ring of the 1,5-benzoxathiepin skeleton also influenced the biological activities. Introduction of the methoxy group into the 7-position (**17b**) resulted in marked enhancement of the activity, whereas shift of the methoxy group from the 7- to the 8-position diminished the effect. Substituents of the amino group in the side chain also caused changes (**17b**,**20b**—**35b**) in the structure–activity relationships. The nitrogen atom attached to the 4-propyl group might play an important role in the interaction with S_2-receptors since the 4-phenylpiperidyl derivative (*cis*-**25b**) showed activity comparable to that of the *N*-phenylpiperazinyl derivative (*cis*-**17b**). The presence of the aromatic ring within a distance of two or three methylenic chains from the nitrogen atom described above seemed to be preferable for S_2-receptor-blocking activity. Among the stereochemical isomers, the *cis*-isomers, rather than the *trans*-isomers, showed more potent and more selective antagonism toward S_2-receptors over adrenergic α_1-receptors. When the 3-(4-phenyl-1-piperazinyl)propyl moiety was introduced into the 2-position, the presence of the methoxy group at the 8-position (*cis*-**43c**) instead of the 7-position (**43b**) was critical for the manifestation of biological activities. On the other hand, substitution of the 3-(4-phenyl-1-piperazinyl)propyl group at the 3-position (**46**) resulted in a marked reduction of S_2-receptor-blocking activity and considerably increased inhibitory potency for adrenergic α_1-receptors. In the series of methyl aminoalkyl-substituted 3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates, methyl *cis*-3-hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate hydrochloride (*cis*-**17b**, CV-5197) showed the most potent S_2-receptor-blocking activity and the highest selectivity over the adrenergic α_1-blocking activity. Some modifications of the 3-hydoxy and 4-ester groups of *cis*-**17b** gave the following results. The activities were unchanged upon modifications of the 3-hydroxy group, *e.g.*, *O*-acetate (*cis*-**59b**) and *N*-methylcarbamoyloxy (*cis*-**60b**) derivatives and the 3-carbonyl compound (**7b**). Removal of the 4-ester moiety gave quite different results in different stereochemical isomers. The *cis*-isomer (*cis*-**50b**) showed activities comparable to those of *trans*-**17b**. However, the S_2-receptor-blocking activity of *trans*-**50b** was 100 times less potent than that of *cis*-**17b** in spite of the configurational retention of the 3-hydroxy and 4-aminoalkyl moieties in both molecules. Removal of the 3-hydroxy and 4-ester groups (**58**) resulted in further reduction of the activity. Ring-contraction of 1,5-benzoxathiepin skeleton (**52** and **53**) resulted in loss of S_2-receptor antagonistic activity. In the series of skeletal modifications, methyl *cis*-3-hydroxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-**74**) showed almost equipotent activity to the corresponding 1,5-benzoxathiepin derivative (*cis*-**17a**). However, introduction of the methoxy group (*cis*-**75**) did not produce the potentiation of the activity that was observed in the case of the 1,5-benzoxathiepins (**17a**→**17b**), and the inhibitory potency of the 1-benzoxepin derivative (*cis*-**73**) was 10 times less than that of *cis*-**17b** in spite of the conformational similarity between the two compounds (Fig. 1). These results suggest that the oxygen atom in the 1,5-benzoxathiepin ring of *cis*-**17b**

might also play a significant role in the interaction with S_2-receptors.

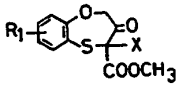
X-Ray crystallographic analyses of known S_2-receptor antagonists have shown that ketanserin,[18] metergoline,[19] pipanperon,[20] and haloperidol[21] have a common extended conformation, but spiperone, with the neuroleptics displaying dopamine-blocking activity and potent S_2-receptor-blocking activity as well, had the folded conformation.[22] A recent investigation by Azibi *et al.* showed the conformational flexibility of spiperone and confirmed the existence of extended and folded conformers in two polymorphs of spiperone by X-ray analysis.[23] The structure–activity relationships in our study indicate that the favorable structure interacting with S_2-receptors approximates the folded conformation proposed as the preferred form of spiperone.[24] A consideration of the folded conformation shown by the X-ray analysis of *cis*-**17b** (CV-5197) suggests that two aromatic rings, a 7-methoxy group, a 3-quasi-axial hydroxy group along with the oxygen atom in the skeleton and the essential nitrogen atom attached to the 4-propyl side chain are significant for the biological activity.

Further evaluation of CV-5197 revealed higher selectivity for the S_2 binding sites than the S_1 ones in the radioligand binding assay in rat brain synaptosomes and practically no inhibitory action on any other agonist, including histamine and acetylcholine.[25] The detailed pharmacological profiles of CV-5197 and its actions on circulatory disorders in experimental animal models will be described elsewhere.[26]

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were obtained with Hitachi 215 and 260-10 spectrophotometers. ^{1}H-NMR spectra were measured with Varian T-60, EM-390, and JEOL JNM-GX400 NMR spectrometers and the 60 MHz spectral data are given, unless otherwise mentioned. Mass spectra (MS) were taken on JEOL JMS-01SC and Hitachi M-80A (high-resolution MS)

TABLE VII. Physicochemical Properties of Methyl 4-Substituted 3-Oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (2—5)



Compd. No.	R_1	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
2b	7-OCH_3	$(CH_2)_3Cl$	44	64—65	$C_{15}H_{17}ClO_5S$	52.33 (52.25	5.10 4.97)	
2c	8-OCH_3	$(CH_2)_3Cl$	42	Oil	$C_{15}H_{17}ClO_5S$	52.33 (52.14	5.10 5.23)	
2d	7-Cl	$(CH_2)_3Cl$	32	Oil	$C_{14}H_{14}Cl_2O_4S$	48.15 (48.36	4.04 4.27)	
2e	7-CH_3	$(CH_2)_3Cl$	37	Oil	$C_{15}H_{17}ClO_4S$	54.79 (54.52	5.21 5.48)	
2f	7-OCH_2Ph	$(CH_2)_3Cl$	36	88—89	$C_{21}H_{21}ClO_5S$	59.93 (59.89	5.03 5.02)	
3b	7-OCH_3	$(CH_2)_4Br$	32	Oil	$C_{16}H_{19}BrO_5S$	47.65 (47.39	4.75 4.86)	
4b	7-OCH_3	$(CH_2)_5Br$	31	Oil	$C_{17}H_{21}BrO_5S$	48.92 (48.81	5.07 5.26)	
5b	7-OCH_3	CH_2CON⟨⟩NPh	69	146—148	$C_{24}H_{26}N_2O_6S$	61.26 (61.40	5.57 5.60	5.94 5.90)

mass spectrometers. In the NMR spectra, chemical shifts are given in the δ (ppm) scale with tetramethylsilane as an internal standard.

Reactions were run at room temperature unless otherwise noted, and followed by TLC on Merck F-254 silicagel plates. Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. The organic extract was washed with water (H_2O). The extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Chromatographic separation was done on Merck Silica gel 60 with the indicated eluant.

Methyl 4-(ω-Halogenoalkyl)-3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (2—5, Table VII)——A typical example of the experimental procedure used to obtain **2**—**5** is as follows. A mixture of methyl 7-methoxy-3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (**1b**) (2.0 g, 7 mmol), 1-bromo-3-chloropropane (2.3 g, 15 mmol), K_2CO_3 (1.5 g, 11 mmol), KI (1.2 g, 7 mmol) and CH_3CN (30 ml) was refluxed with stirring under an N_2 stream for 3 h. After filtration of the reaction mixture, the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and worked up (AcOEt; H_2O). The residue was subjected to column chromatography on silica gel (hexane : CH_2Cl_2 : AcOEt = 30 : 15 : 1). Compound **2b** (1.12 g, 44%) was obtained from the first fraction as colorless prisms (recrystallized from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1760, 1725, 1600, 1485, 1260, 1240, 1210, 1175, 1040. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.2 (4H, m), 3.57 (2H, t, J = 6 Hz, CH_2Cl), 3.73 (3H, s), 3.75 (3H, s), 4.47 (1H, d, J = 18 Hz, C_2-H), 4.73 (1H, d, J = 18 Hz, C_2-H), 6.55 (1H, dd, J = 8, 2 Hz, C_8-H), 6.57 (1H, d, J = 2 Hz, C_6-H), 6.88 (1H. d, J = 8 Hz, C_9-H).

The second fraction yielded methyl 3-(3-chloropropyloxy)-7-methoxy-2*H*-1,5-benzoxathiepin-4-carboxylate. (0.38 g, 15%) as a colorless oil. MS *m/z*: 344, 346 (M^+). IR ν_{max}^{neat} cm^{-1}: 1720 (ester). ^{1}H-NMR ($CDCl_3$) δ: 2.18 (2H, m), 3.70 (2H, t, J = 6 Hz, CH_2Cl), 3.72 (3H, s), 3.80 (3H, s), 4.10 (2H, t, J = 6 Hz, $O\underline{CH_2}CH_2$), 5.10 (2H, s, C_2-H). Compounds **2**—**5** were prepared by similar alkylation of **1a**—**f** with the corresponding ω-halogenoalkylbromides, and their physical data are listed in Table VII.

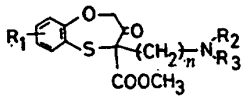
Methyl *cis*- and *trans*-3-Hydroxy-7-methoxy-4-[2-oxo-2-(4-phenyl-1-piperazinyl)ethyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (*cis*- and *trans*-6b)——$NaBH_4$ (0.38 g, 10 mmol) was added in small portions to a solution of **5b** (3.1 g, 6.7 mmol) in MeOH (50 ml). The mixture was stirred for 1 h and then poured into ice-H_2O. The resulting precipitates were collected by filtration and recrystallized from AcOEt to give *cis*-**6b** (1.8 g, 57%) as colorless prisms, mp 213—215 °C. *Anal.* Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93. Found: C, 60.87; H, 5.84; N, 5.86. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1740 (ester), 1650 (amide). ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 3.907 (1H, dd, J = 1.2, 13.2 Hz, C_2-H), 4.128 (1H, dd, J = 1.2, 4.4 Hz, C_3-H), 4.341 (1H, dd, J = 4.4, 13.2 Hz, C_2-H). Chromatographic purification of the mother liquor gave *trans*-**6b** (0.4 g, 13%) as a colorless oil, which was converted into the hydrochloride, colorless crystals, mp 170—180 °C (dec.). *Anal.* Calcd for $C_{24}H_{28}N_2O_6S \cdot HCl \cdot 1/2H_2O$: C, 55.64; H, 5.83; N, 5.40. Found: C, 55.38; H, 5.73; N, 5.44. IR ν_{max}^{KBr} cm^{-1}: 3550, 1740, 1650. ^{1}H-NMR(400 MHz) (DMSO-d_6) δ: 4.082 (1H, dd, J = 5.7, 12.6 Hz, C_2-H), 4.185 (1H, ddd, J = 2.2, 5.7, 7.3 Hz, C_3-H), 4.300 (1H, dd, J = 2.2, 12.6 Hz, C_2-H), 5.546 (1H, d, J = 7.3 Hz, OH).

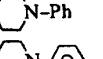
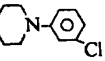
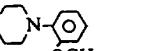
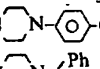
Methyl 4-Aminoalkyl-Substituted 3-Oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (7—14, Table VIII)——A typical example of the experimental procedure used to obtain **7**—**14** is as follows. Method A) A mixture of **2b** (56 g, 0.16 mol), *N*-phenylpiperazine (40 g, 0.26 mol), K_2CO_3 (34 g, 0.25 mol), KI (5.5 g, 33 mmol) and DMF (250 ml) was stirred at 70 °C for 7 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was worked up and the residue was recrystallized from MeOH to give **7b** (57 g, 75%) as colorless crystals. IR ν_{max}^{KBr} cm^{-1}: 1755 (ester), 1720 (CO), 1600. 1485, 1265, 1240, 1225, 1205, 1045. ^{1}H-NMR ($CDCl_3$) δ: 1.2—3.3 (14H, m), 3.68 (3H, s), 3.72 (3H, s), 4.38 (1H, d, J = 18 Hz, C_2-H), 4.72 (1H, d, J = 18 Hz, C_2-H), 6.4—7.4 (8H, m). Method B) A mixture of **1b** (5 g, 19 mmol), 3-(4-phenyl-1-piperazinyl)propyl chloride (6.7 g, 28 mmol), K_2CO_3 (4.65 g, 34 mmol), KI (3 g, 18 mmol) and CH_3CN (150 ml) was refluxed with stirring for 4 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and extracted with AcOEt. The organic layer was worked up and the residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give **7b** (2.7 g, 31%) as colorless crystals. Compounds **7**—**14** were similarly prepared by the substitution of **2**—**4** with the corresponding amines (method A) or by the alkylation of **1** with 3-(4-phenyl-1-piperazinyl)propyl chloride (method B), and their physical data are listed in Table VIII.

Methyl *cis*- and *trans*-4-(3-Chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (*cis*- and *trans*-15b)——$NaBH_4$ (0.3 g, 8 mmol) was added in small portions to an ice-cooled solution of **2b** (2.0 g, 6 mmol) in MeOH (15 ml) and THF (8 ml) with stirring. The mixture was stirred for 1 h, then poured into ice-H_2O and worked up (AcOEt; H_2O). The residue was subjeced to column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give *trans*-**15b** (0.5 g, 25%) from the first fraction, as colorless needles, mp 108—110 °C (recrystallized from AcOEt–hexane). *Anal.* Calcd for $C_{15}H_{19}ClO_5S$: C, 51.95; H, 5.52. Found: C, 51.63; H, 5.51. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1730 (ester). ^{1}H-NMR ($CDCl_3$) δ: 1.95 (4H, m, $C\underline{H_2}C\underline{H_2}CH_2Cl$), 3.48 (2H, t, J = 6.5 Hz, $C\underline{H_2}Cl$), 3.58 (3H, s), 3.70 (3H, s), 4.0—4.2 (3H, m).

The second fraction yielded *cis*-**15b** (1.25 g, 63%) as colorless prisms, mp 80—82 °C (recrystallized from EtOH). *Anal.* Calcd for $C_{15}H_{19}ClO_5S$: C, 51.95; H, 5.52. Found: C, 51.61; H, 5.48. IR ν_{max}^{KBr} cm^{-1}: 3540 (OH), 1735 (ester), 1600, 1485, 1440, 1250, 1210. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.4 (4H, m), 3.40 (2H, t, J = 4 Hz, CH_2Cl), 3.75 (3H, s), 3.80

TABLE VIII. Physicochemical Properties of Methyl 4-Aminoalkyl-Substituted 3-Oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (7—14)



Compd. No.	R_1	n	$N<^{R_2}_{R_3}$	Method	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
7a	H	3		B	18	176—178	$C_{24}H_{28}N_2O_4S\cdot HCl\cdot 1/2\,H_2O$	59.67 (59.49)	6.26 (6.33)	5.83 (5.79)
7b	7-OCH_3	3		A B	75 31	110—112	$C_{25}H_{30}N_2O_5S$	63.81 (63.50)	6.43 (6.37)	5.95 (5.71)
7c	8-OCH_3	3		B	32	140—145	$C_{25}H_{30}N_2O_5S\cdot 2HCl\cdot H_2O$	53.47 (53.55)	6.10 (5.87)	4.99 (5.00)
7d	7-Cl	3		A B	76 27	197—199	$C_{24}H_{27}ClN_2O_4S\cdot 2HCl\cdot 1/2\,H_2O$	51.76 (52.02)	5.43 (5.12)	5.03 (5.08)
7e	7-CH_3	3		A B	78 29	145—150	$C_{25}H_{30}N_2O_4S\cdot 2HCl\cdot 1/2\,H_2O$	55.96 (56.11)	6.20 (6.19)	5.22 (5.11)
8b	7-OCH_3	3		A	73	153—156	$C_{25}H_{29}N_2O_5S\cdot 2HCl$	51.95 (51.85)	5.41 (5.42)	4.85 (4.74)
9b	7-OCH_3	3		A	75	185—190	$C_{26}H_{32}N_2O_6S\cdot 2HCl$	54.45 (54.46)	5.98 (5.94)	4.89 (4.83)
10b	7-OCH_3	3		A	76	133—135	$C_{26}H_{32}N_2O_5S\cdot 1/2\,H_2O$	61.27 (60.95)	6.26 (6.30)	5.50 (5.48)
11b	7-OCH_3	3		A	62	152—155	$C_{32}H_{36}N_2O_5S\cdot 2HCl\cdot 2^1/_2\,H_2O$	56.63 (56.64)	6.39 (6.16)	4.13 (4.15)
12b	7-OCH_3	3		A	58	158—162	$C_{24}H_{29}N_3O_5S\cdot 2HCl\cdot 1^1/_2\,H_2O$	50.44 (50.69)	5.99 (5.81)	7.35 (7.30)
13b	7-OCH_3	4		A B	49 22	155—165	$C_{26}H_{32}N_2O_5S\cdot 2HCl\cdot 1/2\,H_2O$	55.12 (55.30)	6.22 (6.19)	4.95 (4.96)
14b	7-OCH_3	5		A B	44 18	130—150	$C_{27}H_{34}N_2O_5S\cdot 2HCl\cdot 1/2\,H_2O$	55.85 (56.00)	6.42 (6.41)	4.83 (4.81)

(3H, s), 3.7—4.4 (3H, m), 6.80 (1H, dd, J=2, 4 Hz, C_7-H), 6.9—7.1 (2H, m). Similar $NaBH_4$ reduction of **2f** gave *cis*- and *trans*-**15f**, respectively.

Methyl *cis*-7-Benzyloxy-4-(3-chloropropyl)-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-15f)——Yield 50%. Colorless oil. *Anal.* Calcd for $C_{21}H_{23}ClO_5S$: C, 59.64; H, 5.48. Found: C, 59.77; H, 5.39.

Methyl *trans*-7-Benzyloxy-4-(3-chloropropyl)-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*trans*-15f)——Yield 30%. Colorless prisms, mp 97—99 °C (recrystallized from AcOEt–hexane). *Anal.* Calcd for $C_{21}H_{23}ClO_5S$: C, 59.64; H, 5.48. Found: C, 59.80; H, 5.51.

Methyl *cis*-3-Hydroxy-7-methoxy-4-[2-(4-phenyl-1-piperazinyl)ethyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-16b)——AcOH (0.48 g, 8 mmol), was added to a suspension of $NaBH_4$ (0.30 g, 8 mmol) in THF (20 ml). The mixture was gently boiled for 0.5 h, and then *cis*-**6b** (0.5 g, 7 mmol) was added to the above mixture. The mixture was refluxed for 20 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give *cis*-**16b** (0.20 g, 42%) as a colorless oil, which was converted into the hydrochloride, *cis*-**16b**·2HCl, colorless crystals (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 3520, 1740 (ester). ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 4.022 (1H, dd, J=2.7, 12.7 Hz, C_2-H), 4.080 (1H, dd, J=2.7, 6.1 Hz, C_3-H), 4.168 (1H, dd, J=6.1, 12.7 Hz, C_2-H).

Methyl 4-Aminoalkyl-Substituted 3-Hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (17—36, Table I)——Method C) $NaBH_4$ (0.51 g, 13.5 mmol) was added in small portions to an ice-cooled solution of **7b** (12.6 g, 27 mmol) in MeOH (100 ml) and THF (30 ml) with stirring. The mixture was stirred for 3 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was worked up. The residue obtained was subjected to column chromatography on silica gel (hexane : AcOEt = 2 : 1—1 : 3). *trans*-**17b** was obtained from the

first fraction as a pale yellow oil, which was isolated as the hydrochloride, *trans*-**17b**·HCl (4.6 g), colorless prisms (recrystallized from 50% EtOH). IR ν_{max}^{KBr} cm^{-1}: 3530, 3500—3200, 2700—2300, 1720, 1600, 1485, 1255, 1235, 1205, 1035. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 3.667 (3H, s), 3.746 (3H, s), 3.794 (1H, dd, J=8.4, 12.7 Hz, C_2-H), 4.107 (1H, dd, J=3.8, 12.7 Hz, C_2-H), 4.383 (1H, dd, J=3.8, 8.4 Hz, C_3-H).

The second fraction yielded *cis*-**17b** as a colorless oil, which was converted into the hydrochloride, *cis*-**17b**·HCl (6.9 g), colorless prisms (recrystallized from 50% EtOH). IR ν_{max}^{KBr} cm^{-1}: 3600—3300, 1735, 1720, 1595, 1480, 1250. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 3.693 (3H, s), 3.758 (3H, s), 3.873 (1H, dd, J=0—1, 13.1 Hz, C_2-H), 3.999 (1H, dd, J=0—1, 4.6 Hz, C_3-H), 4.155 (1H, dd, J=4.6, 13.1 Hz, C_2-H). Method D) A mixture of *cis*-**15b** (95 g, 0.20 mol), *N*-phenylpiperazine (50 g, 0.33 mol), K_2CO_3 (42 g, 0.31 mol) and DMF (400 ml) was stirred at 70 °C for 8 h. The reaction mixture was worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 3) to give *cis*-**17b**, which was isolated as the hydrochloride (83.7 g, 56%).

Compounds **17**—**36** were similarly prepared by method C or method D, and their physicochemical properties are listed in Table I.

Methyl *cis*-3,7-Dihydroxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-17g, Table I)——Method E) Pd black (1.0 g) was added to a solution of *cis*-**17f** (2.45 g), conc. HCl (1.1 ml), and MeOH (200 ml). The mixture was hydrogenated under atmospheric pressure of H_2 for 20 h. After filtration of the catalyst, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt : MeOH = 30 : 30 : 1), followed by recrystallization from AcOEt to give *cis*-**17g** (1.31 g, 64%) as colorless crystals. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1730 (ester). ^{1}H-NMR ($CDCl_3$) δ: 1.1—3.4 (14H, m), 3.72 (3H, s, $COOCH_3$). 4.0—4.1 (3H, m), 6.6—7.4 (8H, m). MS *m/z*: 458 (M^+).

Similarly, catalytic hydrogenation of *cis*-**36f** and *cis*-**37f** gave *cis*-**38g** and *cis*-**39g** (Table I), respectively.

Methyl *cis*-7-Benzyloxy-3-hydroxy-4-(3-piperazinylpropyl)-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-37f, Table I)——A mixture of *cis*-**15f** (2.0 g, 4.7 mmol), *N*-*tert*-butyloxycarbonylpiperazine (1.76 g, 9.5 mmol), K_2CO_3 (0.98 g, 7 mmol), KI (0.4 g, 2.4 mmol) and CH_3CN (20 ml) was refluxed for 6 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was purified by column chromatography on silica gel (hexane : AcOEt = 3 : 2) to give the *tert*-butyloxycarbonyl derivative of *cis*-**37f** (1.8 g, 69%) as a colorless oil. MS *m/z*: 572 (M^+), which was treated with HCl–AcOEt to give *cis*-**37f** (1.6 g) as colorless prisms (recrystallized from MeOH). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1730 (ester). ^{1}H-NMR (DMSO-d_6) δ: 1.2—2.4 (6H, m), 3.40—3.60 (8H, m), 3.68 (3H, s, $COOCH_3$), 3.9—4.1 (3H, m), 5.16 (2H, s, CH_2Ph), 6.7—7.5 (8H, m).

Methyl *cis*- and *trans*-3-(3-Hydroxy-7-methoxy-3,4-dihydro)2*H*-1,5-benzoxathiepin-2-yl)propionate (*cis*- and *trans*-41b)——$NaBH_4$ (0.2 g, 5.3 mmol) was added in small portions to a solution of **40b**[1] (2.0 g, 6.7 mmol) in MeOH (20 ml) and THF (20 ml) with stirring. The mixture was stirred for 3 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was worked up. The residue was subjected to column chromatography on silica gel (hexane : CH_2Cl_2 : AcOEt = 3 : 3 : 1) to give *cis*-**41b** (0.94 g, 47%) from the first fraction, as colorless crystals, mp 88—89 °C (recrystallized from Et_2O-petroleum ether). *Anal.* Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.50; H, 6.04. IR ν_{max}^{KBr} cm^{-1}: 3490 (OH), 1730 (ester). ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 2.950 (1H, dd, J=2.0, 14.3 Hz, C_4-H), 3.000 (1H, dd, J=5.0, 14.3 Hz, C_4-H), 3.574 (1H, ddd, J=0—1, 3.3, 10.4 Hz, C_2-H), 3.966 (1H, ddd, J=0—1, 2.0, 5.0 Hz, C_3-H).

From the second fraction, *trans*-**41b** (0.72 g, 36%) was obtained as colorless crystals, mp 65—66 °C (recrystallized from Et_2O–petroleum ether). *Anal.* Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.48; H, 6.10. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH). 1725 (ester). ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 2.739 (1H, dd, J=4.6, 14.6 Hz, C_4-H), 3.558 (1H, dd, J=2.6, 14.6 Hz, C_4-H), 3.910 (1H, ddd, J=2.4, 6.0, 8.0 Hz, C_2-H), 3.950 (1H, ddd, J=2.6, 4.6, 8.0 Hz, C_3-H).

Methyl *cis*-(3-Hydroxy-8-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-2-yl)propionate (*cis*-41c)——$NaBH_4$ reduction of **40c** as described for **40b** gave *cis*-**41c** (86% yield) as a colorless oil. *Anal.* Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.55; H, 6.19. IR ν_{max}^{neat} cm^{-1}: 3480 (OH), 1730 (ester).

***cis*-7-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-42b)**——A mixture of *cis*-**41b** (300 mg, 1 mmol) and *N*-phenylpiperazine (1 ml) was stirred at 90 °C for 3 h. The reaction mixture was worked up (AcOEt; H_2O). The residue was recrystallized from AcOEt–Et_2O to yield *cis*-**42b** (320 mg, 74%) as colorless crystals, mp 110—111 °C. *Anal.* Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.62; H, 6.51; N, 6.52. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1645 (amide).

Similar amidation of *trans*-**41b** and *cis*-**41c** gave *trans*-**42b** and *cis*-**42c**, respectively.

***trans*-7-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*trans*-42b)**——Yield 75%. Recrystallization from AcOEt gave colorless crystals, mp 139—140 °C. *Anal.* Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.52; H, 6.31: N, 6.61.

***cis*-8-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-42c)**——Yield 71%. Colorless prisms, mp 126—127 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.31; N, 6.61. Found: C, 64.30; H, 6.60; N, 6.43.

***cis*-7-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-43b)**——A solution of *cis*-**42b** (350 mg, 0.8 mmol) in THF (10 ml) was added dropwise to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol)

in dry Et_2O (20 ml) with stirring under an atmosphere of dry N_2. The mixture was refluxed for 3 h. The reaction mixture was diluted with 20% NaOH and filtered off. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give *cis*-**43b** (270 mg, 80%) as colorless crystals, mp 107—109 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.59; H, 7.22; N, 6.90. IR ν_{max}^{KBr} cm^{-1}: 3450—3300 (OH), 1585, 1475, 1230, 1030, 915. ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 2.953 (1H, dd, J = 2.1, 14.2 Hz, C_4-H), 3.039 (1H, dd, J = 5.4, 14.2 Hz, C_4-H), 3.609 (1H, ddd, J = 0—1, 4.0, 9.6 Hz, C_2-H), 3.975 (1H, ddd, J = 0—1, 2.1, 5.4 Hz, C_3-H).

Similar $LiAlH_4$ reduction of *trans*-**42b** and *cis*-**42c** gave *trans*-**43b** and *cis*-**43c**, respectively.

***trans*-7-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*trans*-43b)**——Yield 77%. Recrystallization from AcOEt gave colorless crystals, mp 128—130 °C. *Anal.* Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.50; H, 6.94; N, 6.56. IR ν_{max}^{KBr} cm^{-1}: 3450—3000 (OH), 1585, 1490, 1235, 1035. ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 2.735 (1H, dd, J = 4.8, 14.5 Hz, C_4-H), 3.534 (1H, dd, J = 2.3, 14.5 Hz, C_4-H), 3.96 (2H, m, C_2-H, C_3-H).

***cis*-8-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-43c)**——Yield 76%. Recrystallization from AcOEt gave colorless prisms, mp 149—150 °C. *Anal.* Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.71; H, 7.26; N, 6.79. IR ν_{max}^{KBr} cm^{-1}: 3400—3200 (OH), 1595, 1475, 1290, 1240, 1160, 1005. ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 2.886 (1H, dd, J = 2.1, 14.2 Hz, C_4-H), 2.966 (1H, dd, J = 5.4, 14.2 Hz, C_4-H), 3.668 (1H, ddd, J = 0—1, 4.0, 9.4 Hz, C_2-H), 3.970 (1H, dd, J = 0—1, 2.1, 5.4 Hz, C_3-H).

3-[2-(1,3-Dioxolan-2-yl)ethyl]-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (45)——A solution of **44**[1] (2.0 g, 9.5 mmol) in THF (10 ml) was added dropwise to a solution of Grignard reagent prepared from Mg (350 mg, 14 mmol), 2-(1,3-dioxolan-2-yl)ethyl bromide (2.6 g, 14 mmol) and THF (30 ml) with stirring. The mixture was stirred for 1 h. The reaction mixture was diluted with 1 N NaOH (20 ml) and worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et_2O = 5 : 1) to give **45** (2.44 g, 82%) as a colorless oil. *Anal.* Calcd for $C_{15}H_{20}O_5S$: 57.67; H, 6.45. Found: C, 57.41; H, 6.52. IR ν_{max}^{neat} cm^{-1}: 3230 (OH), 1595, 1490, 1475, 1195. ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 1.6—1.8 (4H, m), 2.83 (2H, s, C_4-H), 3.75 (3H, s, OCH_3), 3.6—4.2 (6H, m), 5.93 (1H, t, J = 3 Hz, $CH\langle^{O}_{O}$). MS *m/z*: 312 (M^+).

7-Methoxy-3-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (46)——A 50% H_2SO_4 solution (2 ml) was added to a solution of **45** (2.9 g, 9.3 mmol) in acetone (20 ml) and H_2O (10 ml). The mixture was stirred for 3 h. The reaction mixture was concentrated to *ca.* 10 ml *in vacuo* and extracted with CH_2Cl_2. The organic layer was worked up and the residue was dissolved in CH_3CN (20 ml). *N*-Phenylpiperazine (1.6 g, 10 mmol) was added to the above solution, the mixture was stirred for 10 h, and then $NaBH_3CN$ (130 mg, 20 mmol) and MeOH were added. The reaction mixture was stirred for 3 h, then diluted with 3 N HCl (10 ml) and stirred for 2 h. The mixture was washed with AcOEt. The aqueous layer was made alkaline with 3 N NaOH (20 ml) and extracted with AcOEt. The organic layer was worked up and the residue was purified by column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give **46** as a colorless oil, which was converted into the hydrochloride, **46**·HCl (2.4 g, 57%), colorless plates, mp 216—219 °C (recrystallized from 50% EtOH). *Anal.* Calcd for $C_{23}H_{30}N_2O_3S \cdot HCl$: C, 61.25; H, 6.93; N, 6.21. Found: C, 61.43; H, 6.70; N, 6.27. IR ν_{max}^{KBr} cm^{-1}: 3500—3200 (OH), 1595, 1485. ^{1}H-NMR (90 MHz) (DMSO-d_6) δ: 1.6—2.1 (4H, m), 2.90 (2H, s, C_4-H), 3.2—4.0 (10H, m), 3.67 (3H, s, OCH_3), 3.93 (2H, s, C_2-H).

4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (47b)——A mixture of **2b** (5.0 g, 14.5 mmol), LiCl (1.5 g, 35 mmol), H_2O (0.3 ml) and DMSO (30 ml) was stirred at 100 °C for 5 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give **47b** (2.0 g, 48%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{15}ClO_3S$: C, 54.45; H, 5.27. Found: C, 54.90; H, 5.24. IR ν_{max}^{neat} cm^{-1}: 1730, 1595, 1490, 1205. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.4 (4H, m), 3.4—4.0 (3H, m), 3.68 (3H, s, OCH_3), 4.43 (1H, d, J = 17 Hz, C_2-H), 4.75 (1H, d, J = 17 Hz, C_2-H).

***cis*-4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-48b)**——$NaBH_4$ reduction of **47b** in MeOH and THF (5 : 1) and usual work up gave *cis*-**48b** (84% yield) as a colorless oil. *Anal.* Calcd for $C_{13}H_{17}ClO_3S$: C, 54.07; H, 5.93. Found: C, 54.46; H, 6.11. IR ν_{max}^{neat} cm^{-1}: 3450 (OH), 1580, 1485. ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 3.044 (1H, ddd, J = 1.2, 5.6, 8.8 Hz, C_4-H), 3.659 (1H, dd, J = 0.7, 12.5 Hz, C_2-H), 3.903 (1H, ddd, J = 0.7, 1.2, 4.0 Hz, C_3-H), 4.367 (1H, dd, J = 4.0, 12.5 Hz, C_2-H).

7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (49b)——A mixture of **47b** (1.8 g) and *N*-phenylpiperazine (2.4 g) was heated at 100 °C for 1 h. The reaction mixture was worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give **49b** (1.68 g, 65%) as a colorless oil. *Anal.* Calcd for $C_{23}H_{28}N_2O_3S$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.62; H, 6.73; N, 6.68. IR ν_{max}^{neat} cm^{-1}: 1725 (CO), 1595. ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.0 (4H, m), 2.3—2.8 (4H, m), 3.65 (3H, s, OCH_3), 4.42 (1H, d, J = 8 Hz, C_4-H), 4.73 (1H, d, J = 18 Hz, C_2-H), 4.80 (1H, d, J = 18 Hz, C_2-H).

***cis*-7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-50b)**——a) Substitution reaction of *cis*-**48b** with *N*-phenylpiperazine, as described for *cis*-**17b** (method D), gave *cis*-**50b** (42% yield) as

colorless prisms, mp 112—113 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.95; H, 7.34; N, 6.92. IR ν_{max}^{KBr} cm^{-1}: 3500—3000, 1595, 1490, 1440, 1200, 1035. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 3.206 (1H, ddd, J=3.8, 4.6, 8.1 Hz, C_4-H), 3.776 (1H, dd, J=8.5, 12.2 Hz, C_2-H), 4.017 (1H, dd, J=3.8, 12.2 Hz, C_2-H), 4.152 (1H, dt, J=3.8, 8.5 Hz, C_3-H).

b) $NaBH_4$ reduction of **49b** in a solution of THF and MeOH (10 : 1) gave *cis*-**50b** (93% yield). The structure of *cis*-**50b** was determined by X-ray crystallographic analysis (Fig. 1).

***cis*-4-(3-Chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylic Acid (*cis*-51b)**——A 1 N NaOH solution (8 ml, 8 mmol) was added to a solution of *cis*-**16b** (2.0 g, 5.8 mmol) in MeOH (20 ml). The mixture was stirred for 14 h, then poured into ice-H_2O containing conc. HCl (5 ml). The resulting precipitates were collected by filtration and recrystallized from AcOEt to give *cis*-**51b** (1.25 g, 75%) as colorless prisms, mp 174—176 °C. *Anal.* Calcd for $C_{14}H_{17}ClO_5S$: C, 50.53; H, 5.15. Found: C, 50.60; H, 5.12. IR ν_{max}^{KBr} cm^{-1}: 3430, 1740, 1485, 1205, 1035. ^{1}H-NMR (DMSO-d_6) δ: 1.2—2.3 (4H, m), 3.43 (2H, t, J=4 Hz, CH_2Cl), 3.75 (3H, s, OCH_3), 3.7—4.4 (3H, m).

***trans*-4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*trans*-48b)**——*cis*-**51b** (700 mg) was heated at 180 °C for 0.5 h under atmosphere of dry N_2. After cooling, the residue was subjected to column chromatography on silica gel (hexane : CH_2Cl_2 : AcOEt = 3 : 3 : 1) to give *trans*-**48b** (101 mg, 16%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{17}ClO_3S$: C, 54.07; H, 5.93. Found: C, 54.33; H, 6.06. IR ν_{max}^{neat} cm^{-1}: 3450 (OH), 1600, 1485, 1200, 1035.

***trans*-7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*trans*-50b)**——A mixture of *trans*-**48b** (100 mg) and *N*-phenylpiperazine (200 mg) was heated at 90 °C for 2 h. The reaction mixture was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give *trans*-**50b** as a colorless oil, which was converted into the hydrochloride, *trans*-**50b**·2HCl (50 mg, 29%), amorphous powder. *Anal.* Calcd for $C_{23}H_{28}N_2O_3S \cdot 2HCl \cdot H_2O$: C, 56.42; H, 6.85; N, 5.51. Found: C, 56.32; H, 6.75; N, 5.44. IR ν_{max}^{KBr} cm^{-1}: 3400, 2800—2200, 1595, 1490, 1440, 1200, 1035. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 3.031 (1H, ddd, J=3.4, 7.7, 9,3 Hz, C_4-H), 3.785 (1H, ddd, J=2.7, 4.9 7.7 Hz, C_3-H), 3.855 (1H, dd, J=5.0, 12.6 Hz, C_2-H), 4.329 (1H, dd, J=2.8, 12.6 Hz, C_2-H).

Methyl 5-(4-Phenyl-1-piperazinyl)-2-(6-methoxy-1,4-benzoxathian-3-yl)pentanoates (52 and 53)——a) A mixture of TsCl (3.0 g, 16 mmol) in pyridine (3 ml) was added dropwise to an ice-cooled solution of *cis*-**17b** (5.0 g, 11 mmol) in pyridine (15 ml). The mixture was stirred at 0—5 °C for 6 h and then poured into ice-H_2O. The supernatant was removed by decantation and the residue was worked up (AcOEt; H_2O). The residue was subjected to column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give a gummy residue [2.0 g, MS *m/z*: 454 (M^+)]. Catalytic hydrogenation of the product obtained (2.0 g) in AcOEt (20 ml) was carried out in the presence of 5% Pd–C (100 mg) under atmospheric pressure of H_2. After hydrogen absorption had ceased (100 ml), the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give **52** from the first fraction as a colorless oil, which was converted into the hydrochloride, **52**·HCl (360 mg, 7% from *cis*-**17b**), colorless prisms, mp 121—123 °C (recrystallized from 50% EtOH). *Anal.* Calcd for $C_{25}H_{32}N_2O_4S \cdot HCl \cdot H_2O$: C, 58.75; H, 6.90; N, 5.48. Found: C, 58.39; H, 6.79; N, 5.30. IR ν_{max}^{KBr} cm^{-1}: 3500. 3430, 2700—2300, 1730 (ester), 1595, 1485, 1260, 1205, 1195. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 2.730 (1H, ddd, J=3.4, 9.5, 10.0 Hz, $-\underset{|}{C}H\underset{|}{C}OOCH_3$), 3.612 (1H, ddd, J=2.1, 5.4, 9.5 Hz, C_3-H), 4.115 (1H, dd, J=5.4, 12.0 Hz, C_2-H), 4.263 (1H, dd, J=2.1, 12.0 Hz, C_2-H).

The second fraction gave **53** as a colorless oil, which was isolated as the hydrochloride **53**·HCl (320 mg, 6% from *cis*-**17b**). Recrystallization from 50% EtOH gave colorless prisms, mp 152—154 °C. *Anal.* Calcd for $C_{25}H_{32}N_2O_4S \cdot HCl$: C, 60.90; H, 6.75; N, 5.68. Found: C, 60.53; H, 6.83; N, 5.70. IR ν_{max}^{KBr} cm^{-1}: 3520, 3450, 2700—2300, 1725, 1595, 1490, 1440, 1260, 1245, 1200. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 2.805 (1H, ddd, J=3.4, 9.8, 10.5 Hz, $-\underset{|}{C}H\underset{|}{C}OOCH_3$), 3.599 (1H, ddd, J=2.0, 4.2, 9.8 Hz, C_3-H), 4.184 (1H, dd, J=2.0, 12.2 Hz, C_2-H), 4.439 (1H, dd, J=4.2, 12.2 Hz, C_2-H).

b) A mixture of red P (300 mg, 10 mmol). I_2 (90 mg) and AcOH (6 ml) was stirred for 0.5 h. *cis*-**16b** (3.0 g, 8.7 mmol) and H_2O (0.1 ml) were added to the above mixture and the mixture was refluxed for 1 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was subjected to column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give a colorless oil [1.38 g, MS *m/z*: 330, 332 (M^+)], which was heated with *N*-phenylpiperazine (4 ml) at 90 °C for 2 h. The mixture obtained was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give first **52** (isolated as **52**·HCl; 0.46 g, 11% from *cis*-**15b**) and then **53** (isolated as **53**·HCl; 0.38 g, 9% from *cis*-**15b**).

1-Chloro-5-(1,3-dixolan-2-yl)pentan-3-ol (54)——A solution of 3-chloropropanal (3.3 g, 36 mmol) in THF (10 ml) was added to a solution of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide prepared from Mg (1.0 g, 41 mmol), 2-(1,3-dioxolan-2-yl)ethyl bromide (7.5 g, 41 mmol) and THF (20 ml). The mixture was stirred for 2 h, then diluted with 1 N NaOH (20 ml) and worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et_2O = 5 : 1) to give **54** (2.6 g, 73%) as a colorless oil. *Anal.* Calcd for $C_8H_{15}ClO_3$: C, 49.36; H, 7.77. Found: C, 49.55; H, 7.51. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1450, 1415, 1345, 1210, 1040. ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.2 (6H, m), 3.4—4.2 (7H, m), 4.91 (1H, t, J=4 Hz, O–CH–O).

5-(1,3-Dioxolan-2-yl)-3-mesyloxypentyl Benzoate (55)——A mixture of **54** (3.0 g, 15 mmol), sodium benzoate (3.0 g, 21 mmol), KI (1.0 g, 6 mmol), CH_3CN (30 ml) and DMF (20 ml) was stirred at 80 °C for 5 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et_2O = 5 : 1) to give 5-(1,3-dioxolan-2-yl)-3-hydroxypentyl benzoate (1.8 g, 42%) as a colorless oil [MS *m/z*: 280 (M^+)]. MsCl (1.8 g, 6.4 mmol) was added to the alcohol obtained above (1.8 g) in pyridine (10 ml). The mixture was stirred for 2 h, poured into ice-H_2O containing conc. HCl (20 ml) and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et_2O = 5 : 1) to give **55** (0.9 g, 54%) as a colorless oil. MS *m/z*: 358 (M^+), 357. High-resolution MS Calcd for $C_{16}H_{22}O_7S$: 358.1085. Found: 358.1088. IR ν_{max}^{neat} cm^{-1}: 1725, 1710, 1595, 1445, 1350, 1280, 1270, 1175. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.4 (6H, m), 3.08(3H, s, OSO_2CH_3), 3.2—4.2 (4H, m), 4.2—4.6 (3H, m), 4.9—5.1 (1H, t, J = 4 Hz, O–CH–O).

2-[1-(1,3-Dioxolan-2-yl)-5-hydroxy-3-pentyl]thio-4-methoxyphenol (56)——A mixture of **55** (1.4 g, 3.9 mmol), 2-mercapto-4-methoxyphenol (0.8 g, 5 mmol), K_2CO_3 (0.6 g, 4.4 mmol) and acetone (20 ml) was stirred for 15 h and then filtered, and the filtrate was concentrated *in vacuo*. A 1 N NaOH solution (10 ml) was added to a solution of the above residue in MeOH (30 ml). The resulting mixture was stirred for 5 h, neutralized with 1 N HCl and worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give **56** (0.7 g, 43%) as a colorless oil. *Anal.* Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 57.51; H, 7.21. IR ν_{max}^{neat} cm^{-1}: 3450—3200 (OH), 1600, 1480, 1275, 1250, 1220, 1205. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.2 (6H, m), 2.8—3.2 (1H, m), 3.77 (3H, s, OCH_3), 3.6—4.2 (6H, m), 4.90 (1H, t, J = 4 Hz, O–CH–O). MS *m/z*: 314 (M^+), 252, 213, 200, 183.

4-[2-(1,3-Dioxolan-2-yl)ethyl]-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin (57)——Ph_3P (0.85 g, 3.2 mmol) was added to a solution of **56** (0.9 g, 2.9 mmol) and toluene (10 ml) with stirring. Then, a solution of ethyl azodiformate (0.55 g, 3.2 mmol) in toluene (1 ml) was added dropwise to the above mixture. The whole was stirred for 2 h and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give **57** (0.61 g, 71%) as a colorless oil. *Anal.* Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.88; H, 6.71. IR ν_{max}^{neat} cm^{-1}: 1595, 1485, 1435, 1280, 1265, 1200. ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.4 (6H, m), 2.9—3.1 (1H, m, C_4-H), 3.75 (3H, s, OCH_3), 3.7—4.6 (6H, m), 4.88 (1H, t, J = 4 Hz, O–CH–O).

7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin (58)——A mixture of **57** (680 mg, 2.3 mmol), 50% H_2SO_4 (0.5 ml), H_2O (2 ml) and acetone (10 ml) was stirred for 2 h, then the reaction mixture was worked up (AcOEt; H_2O). *N*-Phenylpiperazine (0.4 g, 2.5 mmol) was added to a solution of the residual oil in CH_3CN (10 ml) and the mixture was stirred for 4 h. Then, $NaBH_3CN$ (190 mg, 3 mmol) was added. The reaction mixture was stirred for 4 h and then worked up (AcOEt; H_2O). The resulting residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give **58** as a colorless oil, which was converted into the hydrochloride, **58**·2HCl (550 mg, 51%), white crystals, mp 150—153 °C (recrystallized from 50% EtOH). *Anal.* Calcd for $C_{23}H_{30}N_2O_2S$·2HCl: C, 58.59; H, 6.84; N, 5.94. Found: C, 58.48; H, 6.75; N, 5.64. IR ν_{max}^{KBr} cm^{-1}: 3500—3400, 2600—2200, 1595, 1480.

Methyl *cis*-3-Acetoxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-59b)——Acetylation of *cis*-**17b** with Ac_2O in pyridine gave *cis*-**59b** as colorless prisms, mp 168—170 °C (recrystallized from AcOEt) in 83% yield. *Anal.* Calcd for $C_{27}H_{34}N_2O_6S$: C, 63.01; H, 6.66; N, 5.44. Found: C, 63.01; H, 6.69; N, 5.40. IR ν_{max}^{KBr} cm^{-1}: 1740 (ester). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $OCOCH_3$), 3.62 (3H, s), 3.63 (3H, s).

Methyl *cis*-7-Methoxy-3-*N*-methylcarbamoyloxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-60b)——*cis*-**60b** was prepared by the reaction of *cis*-**17b** with CH_3NCO in DMF and isolated as the hydrochloride in 89% yield. Recrystallization from EtOH gave *cis*-**60b**·2HCl as colorless prisms, mp 167—172 °C. *Anal.* Calcd for $C_{27}H_{35}N_3O_6S$·2HCl: C, 53.82; H, 6.19; N, 6.97. Found: C, 53.56; H, 6.42; N, 6.71. IR ν_{max}^{KBr} cm^{-1}: 3400, 1720 (ester). ^{1}H-NMR (DMSO-d_6–D_2O) δ: 2.75 (3H, s, $NHCH_3$), 3.73 (6H, s, 7-OCH_3 + $COOCH_3$), 5.25 (1H, m, C_3-H).

***cis*-3-Hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylic Acid (*cis*-61b)**——A mixture of *cis*-**17b** (3.0 g, 6.3 mmol), 1 N NaOH (12 ml) and MeOH (40 ml) was stirred at 60 °C for 5 h. After evaporation of the MeOH, the residual mixture was acidified with 1 N HCl. The resulting precipitates were collected by filtration and recrystallized from EtOH to give *cis*-**61b** (2.4 g, 95%) as colorless crystals, mp 250—260 °C (dec.). *Anal.* Calcd for $C_{24}H_{30}N_2O_5S$·H_2O: C, 60.48; 6.77; N, 5.88. Found: C, 60.27; H, 6.73; N, 5.66. IR ν_{max}^{KBr} cm^{-1}: 3600, 3510—3300, 2600—2200, 1640—1590, 1485, 1370, 1210.

Ethyl *cis*-3-Hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate (*cis*-62b)——A mixture of *cis*-**61b** (1.2 g, 2.5 mmol), Et_2SO_4 (0.5 g, 3.2 mmol), $NaHCO_3$ (1.0 g, 12 mmol) and EtOH (25 ml) was refluxed for 3 h, then worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give *cis*-**62b** as colorless oil, which was isolated as the hydrochloride *cis*-**62b**·2HCl (0.5 g, 42%), colorless prisms, mp 186—188 °C (from EtOH). *Anal.* Calcd for $C_{26}H_{34}N_2O_5S$·2HCl: C, 55.81; H, 6.49; N, 5.01. Found: C, 55.74; H, 6.56; N, 5.03. IR ν_{max}^{KBr} cm^{-1}: 3540 (OH), 1740 (ester). ^{1}H-NMR (DMSO-d_6–D_2O) δ: 1.30 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.72 (3H, s, 7-OCH_3), 4.1—4.2 (3H, m, C_2-H + C_3-H), 4.28 (2H, t, J = 7 Hz, $OC\underline{H_2}CH_3$).

***cis*-4-Hydroxymethyl-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-63b)**——A solution of *cis*-**17b** (400 mg, 0.8 mmol) in dry Et_2O (10 ml) was added dropwise to a suspension of $LiAlH_4$ (90 mg, 2.4 mmol) and dry Et_2O (20 ml) with stirring. The mixture was refluxed for 0.5 h. Excess $LiAlH_4$ was decomposed by adding H_2O and 15% NaOH. The inorganic deposit was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from AcOEt to give *cis*-**62** (300 mg, 80%) as colorless needles, mp 163—165 °C. *Anal.* Calcd for $C_{24}H_{32}N_2O_4S$: C, 64.84; H, 7.25; N, 6.30. Found: C, 64.76; H, 7.31; N, 6.39. IR ν_{max}^{KBr} cm^{-1}: 3540 (OH). ^{1}H-NMR (400 MHz) ($CDCl_3$–D_2O) δ: 3.923 (1H, dd, J=1.0, 4.9 Hz, C_3-H), 3.995 (1H, dd, J=1.0, 12.8 Hz, C_2-H), 4.138 (1H, dd, J=4.9, 12.8 Hz, C_2-H).

Methyl 8-Methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (64)——A solution of methyl 3-(4-methoxy-2-methoxycarbonylmethyloxyphenyl)propionate (15 g, 53 mmol) in toluene (200 ml) was added dropwise to a gently boiling suspension of 60% NaH (5.6 g, 140 mmol), *tert*-BuOH (0.4 ml) and toluene (200 ml) (8 h). After refluxing for 0.5 h, the reaction mixture was allowed to stand overnight and then poured into ice-H_2O containing AcOH (10 ml). The organic layer was separated, washed with H_2O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 4 : 1) to give **64** (9.5 g, 71%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{14}O_5S$: C, 62.39; H, 5.64. Found: C, 62.18; H, 5.86. IR ν_{max}^{neat} cm^{-1}: 1760, 1720. ^{1}H-NMR ($CDCl_3$) δ: 2.9—3.1 (4H, m), 3.72 (3H, s), 3.80 (3H, s), 5.00 (1H, s, C_2-H), 6.5—7.2 (3H, m).

Methyl 3-Oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (65)——**65** was prepared in 81% yield by Dieckmann reaction of methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate, as described for **64**. The starting methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate was prepared in 5 steps from methyl 3-(2-hydroxyphenyl)propionate *via* the route involving thiocarbamoylation with dimethylthiocarbamoyl chloride (74% yield), thermal rearrangement at 260—270 °C (70% yield), alkaline hydrolysis, *S*-alkylation with methyl bromoacetate and esterification with dimethyl sulfate (55% yield). Chromatographic purification of the crude product gave **65** as a colorless oil. *Anal.* Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12. Found: C, 61.23; H, 5.28. MS *m/z*: 236 (M^+). IR ν_{max}^{neat} cm^{-1}: 1740, (ester), 1700 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.6—3.4 (4H, m), 3.62 (3H, s, $COOCH_3$), 4.20 (1H, s, C_2-H), 6.9—7.7 (4H, m).

Methyl 8-Methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (66)——**66** was similarly prepared by Dieckmann reaction of methyl 3-(4-methoxy-2-methoxycarbonylmethylthiophenyl)propionate in 80% yield. Recrystallization from AcOEt–hexane gave **66** as colorless prisms, mp 76—78 °C. *Anal.* Calcd for $C_{13}H_{14}O_4S$: C, 58.68; H, 5.30. Found: C, 58.59; H, 5.26. IR ν_{max}^{KBr} cm^{-1}: 1740 (ester), 1710 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.9—3.1 (4H, m), 3.68 (3H, s), 3.78 (3H, s), 4.22 (1H, s, C_2-H), 6.7—7.4 (3H, m).

Methyl 2-(3-Chloropropyl)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (67)——**67** was prepared by alkylation of **64** with 3-bromo-1-chloropropane, as described for **2**. Chromatographic purification gave a colorless oil. MS *m/z*: 326, 328 (M^+). High-resolution MS Calcd for $C_{16}H_{19}ClO_5$: 326.0919. Found: 326.0925. IR ν_{max}^{neat} cm^{-1}: 1750 (ester), 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.2 (4H, m), 2.92 (4H, s, C_4-H + C_5-H), 3.52 (2H, t, J=6 Hz, CH_2Cl), 3.64 (3H, s), 3.72 (3H, s), 6.4—7.1 (3H, m). Compound **67** thus obtained was found to contain a small amount of enol ether (2—3%) as a by-product, but was used for the following step without further purification. **68** and **69** were similarly prepared by alkylation of **65** and **66**, respectively.

Methyl 2-(3-Chloropropyl)-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (68)——A colorless oil (41% yield). MS *m/z*: 312, 314 (M^+). High-resolution MS Calcd for $C_{15}H_{17}ClO_5S$: 312.0586. Found: 312.0582. IR ν_{max}^{neat} cm^{-1}: 1720 (ester, CO). ^{1}H-NMR ($CDCl_3$) δ: 1.7—3.6 (10H, m), 3.65 (3H, s, $COOCH_3$), 7.1—7.8 (4H, m).

Methyl 2-(3-Chloropropyl)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (69)——A colorless oil (50% yield). MS *m/z*: 342, 344 (M^+). High-resolution MS Calcd for $C_{16}H_{19}ClO_4S$: 342.0692. Found: 342.0693. IR ν_{max}^{neat} cm^{-1}: 1740 (ester), 1700 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.0 (4H, m), 2.8—3.0 (4H, m), 3.42 (2H. t, J=7 Hz, CH_2Cl), 3.62 (3H, s), 3.72 (3H, s), 6.7—7.4 (3H, m).

Methyl *cis*- and *trans*-2-(3-Chloropropyl)-3-hydroxy-8-methoxy-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*cis*- and *trans*-70)——$NaBH_4$ reduction of **67** in an ice-cooled solution of THF and MeOH (1 : 4) and subsequent column chromatography on silica gel (hexane : AcOEt = 3 : 1) gave *cis*-**70** (from the first fraction) and *trans*-**70** (from the second fraction).

cis-**70**: A colorless oil (46% yield). *Anal.* Calcd for $C_{16}H_{21}ClO_5$: C, 58.45; H, 6.44. Found: C, 58.66; H, 6.59. IR ν_{max}^{neat} cm^{-1}: 3500 (OH), 1740 (ester). ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.0 (4H, m), 2.4—3.5 (6H, m), 3.72 (3H, s), 3.75 (3H, s), 6.5—7.2 (3H, m).

trans-**70**: A colorless oil (44% yield). *Anal.* Calcd for $C_{16}H_{21}ClO_5$: C, 58.45; H, 6.44. Found: C, 58.78; H, 6.21. IR ν_{max}^{neat} cm^{-1}: 3500 (OH), 1740 (ester). ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.0 (4H, m), 2.4—3.2 (4H, m), 3.48 (2H, t, J=7 Hz, CH_2Cl), 3.66 (3H, s), 3.72 (3H, s), 4.0—4.2 (1H, m), 6.46—7.02 (3H, m).

Methyl *cis*-2-(3-Chloropropyl)-3-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-71)——$NaBH_4$ reduction of **68** gave *cis*-**71** (80% yield) as colorless prisms, mp 108—110 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{15}H_{19}ClO_3S$: C, 57.23; H, 6.08. Found: C, 57.27; H, 6.11. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1730 (ester). ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 4.051 (1H, dd, J=2.7, 5.4 Hz, C_3-H).

Methyl *cis*-2-(3-Chloropropyl)-3-hydroxy-8-methoxy-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-72)——$NaBH_4$ reduction of **69** gave *cis*-**72** (74% yield) as a colorless oil. *Anal.* Calcd for $C_{16}H_{21}ClO_4S$: C, 55.73; H, 6.14.

Found: C, 55.98; H, 6.00. IR ν_{max}^{neat} cm^{-1}: 3530 (OH), 1740. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 4.056 (1H, dd, J=2.7, 5.4 Hz, C_3-H).

Methyl *cis*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*cis*-73, Table II)——A mixture of *cis*-70 (1.0 g, 3.1 mmol), *N*-phenylpiperazine (1.1 g, 6.8 mmol), and KI (0.25 g, 1.5 mmol) was stirred at 90 °C for 3 h. The reaction mixture was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 30 : 20 : 1) to give *cis*-73 (0.65 g, 47%) as colorless prisms (recrystallized from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1760, 1730. ^{1}H-NMR (400 MHz) of *cis*-73·2HCl (DMSO-d_6–D_2O) δ: 4.064 (1H, dd, J=3.4, 3.9 Hz, C_3-H).

Similar treatment of *trans*-70, *cis*-71 and *cis*-72 gave *trans*-73, *cis*-74 and *cis*-75, respectively (Table II).

Methyl *trans*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*trans*-73)——Recrystallization of the hydrochloride from MeOH–Et_2O gave *trans*-73·2HCl as colorless crystals. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 4.070 (1H, dd, J=2.7, 7.3 Hz, C_3-H).

Methyl *cis*-3-Hydroxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-74)——Recrystallization from AcOEt gave *cis*-74 as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3450—3100 (OH), 1720 (ester).

Methyl *cis*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-75)——Recrystallization of the hydrochloride from 30% EtOH gave *cis*-75·HCl as colorless crystals. ^{1}H-NMR (400 MHz) (DMSO-d_6–D_2O) δ: 4.056 (1H, dd, J=2.2, 5.1 Hz, C_3-H).

X-Ray Analyses of *cis*-17b, *cis*-50b, *cis*-58b, *cis*-71 and *cis*-73——All single-crystal measurements were made with a Rigaku AFC-5 automatic diffractometer. The structures were solved by the direct method[27] and refined by a block-diagonal least-squares method[28] using unit weight. In the final refinement, non-hydrogen and hydrogen atoms were refined with anisotropic and isotropic temperature factors, respectively. Details of the X-ray analyses will be published elsewhere.

Serotonin S_2-Receptor-Blocking Activity and Adrenergic α_1-Receptor-Blocking Activity *in Vitro*——Pig hearts were obtained from a slaughterhouse under ice-cooling and the left circumflex or anterior descending coronary artery was dissected out within 3 h after death. The coronary artery was cut into a ring preparation of 3 mm in width. On the other hand, the thoracic aorta was dissected out from albino rabbits (2—3 kg body weight, male) after exsanguination. The rabbit aorta was cut into a spiral preparation of about 2 mm in width and about 2 cm in length. These blood vessel preparations were suspended in organ baths containing 20 ml of Krebs–Henseleit solution with a pair of suspending hooks. One of the hooks was fixed to the bottom of the organ bath, while the other was connected to a strain-gauge transducer, and the tension developed by these preparations was isometrically measured. The organ bath was maintained at 37°C, and the Krebs–Henseleit solution was saturated with a gas mixture of 97% O_2+3% CO_2. As agonists, serotonin (10^{-6} M) and norepinephrine (10^{-7} M) were used in the porcine coronary and rabbit aortic preparations, respectively.

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